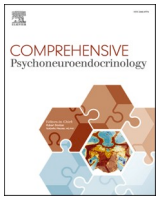
Comprehensive Psychoneuroendocrinology 20 (2024) 100268

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology



Oxytocin in growth, reproduction, restoration and health

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A B S T R A C T

This article summarizes my scientific work and describes some personal experiences during this period. After my basal medical training (MD) (1971), I obtained a PhD in pharmacology (1976) and ended up as a professor of Physiology.

My initial studies were within the field of gastroenterology. I showed that the gastrointestinal hormone gastrin, which stimulates HCL secretion in the stomach, was released in response to stimulation of the vagal nerve. Later I showed that the entire endocrine system of the gastrointestinal (GI) tract that promotes digestion and anabolic metabolism and growth was under vagal nerve control. I also showed that activation of the vagal nerve inhibits the function of the inhibitory substance somatostatin.

10 years later, after some big changes in my personal life, my research focus changed. I became interested in female physiology, particularly the role of oxytocin. In addition, I became aware of the situation of female scientists and started to work with questions regarding equality between women and men.

I gathered a group of interested female medical students and midwives around me. We demonstrated that breastfeeding and touch (e.g., between mother and baby), via stimulation of sensory nerves in the skin, activated the endocrine system of the GI tract and, thereby, anabolic processes and growth. The effects were exerted via a vagal mechanism and involved activation of parvocellular oxytocinergic neurons from the paraventricular nucleus (PVN). We also showed that the gastrointestinal hormone cholecystokinin stimulated the release of oxytocin in a calorie-dependent way via an afferent vagal mechanism.

In summary, there is a bidirectional, vagally mediated connection between the endocrine system of the GI tract and the oxytocin producing neurons in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus.1. Oxytocinergic neurons from the PVN enhances the activity of the endocrine system of the GI tract and thereby growth and regeneration. The effect is exerted via efferent vagal fibers which inhibit the release of somatostatin. 2. Food in the duodenum triggers a release of cholecystokinin (CCK), which via a vagal afferent mechanism stimulates the release and function of oxytocin. This mechanism is not activated in the absence of food intake.

Administration of oxytocin induces a multitude of actions, i.e., anxiolytic and sedative effects, increased pain threshold, lowering of cortisol and blood pressure and an increased activity of the endocrine system of the GI tract. Repeated administration of oxytocin may induce long-term effects and "secondary" mechanisms such as an increased activity of alpha-2- adrenoceptors are involved.

Oxytocin released by suckling during breastfeeding or by touch during social interaction will induce a similar effect spectrum. Activation of the parvocellular neurons will stimulate some aspects of social behavior, induce calm and well-being, and decrease levels of fear, stress, and pain. In addition, vagal functions and the activity of the endocrine system of the GI tract will be stimulated. Together, these effects are consistent with the oxytocin-mediated calm and connection response and, in a long-term perspective, with the promotion of well-being and health.

A second period of professional difficulties occurred in the late 1990s. I moved to the Swedish University of Agriculture, where I started to investigate the role of oxytocin in interactions between humans and pets, as this type of interaction had been shown to promote health. I continued to study the role of oxytocin in female reproduction, in particular, the role of oxytocin during labor and birth and in the peripartum period. In addition, I started to write books about different aspects of oxytocin.

I also wanted to establish a role for oxytocin in the treatment of vaginal atrophy. Several clinical studies show that local intravaginal application of oxytocin in women with vaginal atrophy increases the regeneration of vaginal mucosal cells and function.

1. Introduction

Recently, I received an invitation from Professor Sue Carter to write a summary of my scientific career for a special issue of the journal Comprehensive Psychoneuroendocrinology; **oxytocin - not just a "female hormone".** After some hesitation, I decided to give it a try. This overview summarizes a 50-year scientific career and scientific production, including more than 500 peer-reviewed articles and 30 PhD students, and is therefore quite long. My professional background (MD and PhD in pharmacology) has, like for anybody else, shaped my line of thoughts and the alphabet I am using to describe them. This educational background is somewhat unusual since so many oxytocin researchers nowadays come from the fields of obstetrics, behavioral sciences, or psychology. As I must summarize a very long research story in a limited

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https://doi.org/10.1016/j.cpnec.2024.100268
Received 28 December 2023; Received in revised form 19 September 2024; Accepted 24 September 2024
Available online 30 September 2024

space, I will focus on projects and collaborations that have had a major and positive impact on the development of my knowledge and on the formation of the hypotheses and models regarding the function of oxytocin presented here. Paragraphs containing summaries of my scientific work and personal experiences, which I consider to be relevant to this article, will also be included. I hope that the long story told here might help young researchers (women and men) to navigate the complex scientific world.

2. My background

I was born in 1944 in Lund, a small university city located in the southern part of Sweden. My father was a bright and ambitious young medical doctor and researcher at the Institution of Physiology, and my mother was a housewife. The Swedish Medical Research Council awarded my father a grant of 700 USD to spend a year doing research in Chicago. They traveled with the first cargo ship that went from Sweden to the US in early 1946. This was just one year after the end of the 2nd World War, and Europe lay in ruins. No wonder that the year in America made an enormous and positive impression on both my father and my mother. Scientifically, the stay in the US was a great success for my father; he learned important new techniques, which he brought back and applied in his lab in Lund. In addition, he obtained many important American scientific contacts and friends.

Just a few years after returning from the US, my father got a chair at the Karolinska Institutet (KI) in Stockholm, and my family moved there in 1953. I was very unhappy about this move. I missed my friends and grandparents, and I spoke "skånska," a southern dialect of Swedish, a little bit related to Danish. My new schoolmates in Stockholm thought it sounded funny, and therefore, I didn't speak in school for a year until I had adopted the Stockholm dialect. I played the piano and learned everything about flowers and plants during this lonely period of my life.

I was brought up in a demanding but, in many ways, generous home, full of humor. My parents very often had guests from all parts of the world. My mother was a beautiful, elegant, and charming hostess and a perfect organizer of social events; in fact, both my father and mother were experts in entertaining guests. When I was invited to international conferences, particularly in the US, I was often approached by people who remembered having attended dinners in my home. I have also tried to continue this openness and generosity towards colleagues visiting Sweden myself. I learned how important social communication is within the scientific world.

My parents also supported me, my brother, and my sister, in traveling and learning languages. Every summer holiday, we were sent to England, France, or Germany to study. I remember spending a term in an English boarding school at the age of 14. In many ways, it was a great experience, but a very cold one, since there was hardly any central heating and many windowpanes were lacking in the beautiful countryside mansion house. I then learned how deeply and negatively cold temperatures may impact your mood and life experience.

I liked school and always did my homework. I studied natural science in high school/college and graduated from school in 1963. I started my medical studies in the autumn of the same year. This was not only because I wanted to become a physician, but it was also a career choice that many students with good school marks made at that time. I loved my time in medical school, especially meeting so many people with similar interests. I received my MD exam at Karolinska Institutet in Stockholm in 1970 and became a Licenced Physician in 1971. I practiced as a physician for some years, but I never did a residency to become a specialist in a particular subject.

2.1. The first steps into science

After my first child was born in 1971, I had to rethink my job situation. I was married to a surgeon, who was almost always on call. At that time, there was an unwritten contract between young parents stating that the women/mothers were free to study and work but would also have the full responsibility for the household and the children.

I got the "brilliant" idea that I could do a PhD at a preclinical medical institution, which in Sweden at that time consisted of a 4–5 years long education. It included experimental work and writing and publishing of 4–5 articles, which then had to be summarized in a small book, *the thesis,* which should be defended publicly. I considered that doing a PhD would give me more flexibility than working as a physician in a hospital. It would allow me to take care of the household and children, and, at the same time, it would allow me a forward movement in my professional career.

Indirectly my "scientific life" had begun much earlier. I was intrigued and inspired by my father Börje Uvnäs. He was the professor of the Department of Pharmacology and, for many years, dean of the medical faculty, as well as a member and chairman of the Nobel Prize Committee of the KI. Not that I ever thought of becoming a researcher during my years in school, but I always wondered what it was that caught my father's interest to such an extent that he spent most of his time at work, and if at home, he was almost always writing (except when having guests). But I always enjoyed talking to my father when he had time. We had a similar way of thinking and looking at things.

I contacted my father and told him I might want to do a PhD, possibly at the Department of Pharmacology. He invited me to give it a try. The department of Pharmacology was huge, and a new PhD student was always welcome, since this could further enhance the already large scientific production of the institution. I was assigned a supervisor, Professor Göran Nilsson, who was an expert on the neurohormonal regulation of gastrointestinal functions, which had, in fact, been one of my father's first scientific interests [1]. Göran Nilsson had just returned from a Post Doc period in New York, at the lab of Professors Rosalyn Yalow and Samuel Berson, who had developed the technique of radioimmunosassay, which allowed measurement of very low levels of peptide hormones [2–5]. Göran Nilsson had learned how to perform a radioimmunoassay for the gastrointestinal (GI) hormone gastrin, which he brought to the Department of Pharmacology at the KI in Stockholm [6]. Rosalyn Yalow, was awarded the Nobel Prize in physiology or medicine 1977 for having developed the technique of radioimmunoassay.

3. The PhD thesis (1972–1976)

My doctoral project was initiated in 1972. The subject of my thesis was to investigate how electrical vagal stimulation influences the release of the gastric hormone gastrin and the secretion of gastric acid juice (HCL) in cats. I defended the thesis*"Gastrin release and HCL secretion induced by electrical vagal stimulation"* in 1976 [7].

To study the role of the vagal nerve in gastrin release, I had to learn to perform animal experiments. I learned how to anesthetize cats, perform electrical stimulations of the vagal nerves, collect blood samples from portal and peripheral blood, measure blood flow, and measure HCl production. Professor Göran Nilsson also taught me how to measure gastrin levels with radioimmunoassay.

3.1. Gastrin

Gastrin is a peptide hormone that is produced in the lower part of the stomach, the antrum. Gastrin is released from the antrum and reaches the fundus, or the gastric acid (HCl) producing part of the stomach, via the circulation. There, it stimulates HCl secretion from the parietal cells in the fundic region of the stomach. Gastric acid (HCl) secretion has many important physiological actions. It takes part in the digestive process, e.g., by activating the enzyme pepsin, which is necessary for the degradation of proteins, and it prevents infections by inactivating several types of bacteria and viruses [8,9].

The amino acid sequence of the heptadecapeptide gastrin molecule had been identified by Gregory and Tracy in 1974 [10]. At that time, it

was known that gastrin was released in response to ingestion of food, in particular by the presence of amino acids and small peptides in the antral lumen. In addition, some data suggested that the vagal nerve activity contributed to the release of gastrin [1,11,12], and in dogs, electrical vagal stimulation was shown to release gastrin [13].

My experimental work showed that gastrin was released by electrical stimulation in cats. The data showed that gastrin was released into the portal vein and that gastrin levels rose in peripheral blood in response to electrical vagal stimulation at an intensity of 3–4 Hz, which is supposed to reflect the characteristics of spontaneous firing of the nerves in the autonomic nervous system [14]. The response was peak shaped and dose dependent, but no further release of gastrin occurred after 2000–3000 impulses had been delivered by the electrical stimulation. The gastrin response, which was not blocked by atropine and consequently mediated by a non-cholinergic mechanism, returned after 20 min of rest. Twice as much gastrin was released in response to bilateral vagal nerve stimulation (Fig. 1) [15,16].

In contrast to the very short-lasting effect on gastrin release induced by electrical vagal stimulation, the secretion of HCl continued as long as the vagal stimulation was ongoing, suggesting a complex interaction between the hormone gastrin and vagal nerve activity regarding activation of HCl secretion. In addition, gastrin was cleared from the acid producing mucosa in connection with the production of HCl [17].

With the help of my Danish colleague Professor Jens Rehfeld, the different molecular forms of gastrin were identified. The cat was found to have an unusual pattern of molecular forms of gastrin in the circulation. Large amounts of a 14 amino acid long variant of gastrin, mini gastrin, rarely seen in other species, were demonstrated. Gastrin-17 was, however, like in other species, the most common molecular variant of gastrin in circulating blood [18].

3.1.1. *Gastrin and vagal nerve activity together stimulate HCl secretion*

Vagal activation stimulates HCl secretion in two different ways: by a direct stimulation of the cholinergic receptors on the parietal cells located in the fundus of the stomach and via gastrin, released into the circulation from the antral part of the stomach in response to vagal nerve activity [15,16]. Gastrin, in turn, stimulates HCl secretion in two ways: by activation of gastrin receptors in the parietal cells and by histamine released from enterochromaffin-like (ECL) cells in the oxyntic/fundic mucosa. Histamine reaches the parietal cells by diffusion and activates HCl secretion by H2 receptors [17,19]. In addition, gastrin exerts trophic effects on the gastric mucosa (Fig. 2) [19].

If HCl secretion is induced by vagal stimulation or infusions of gastrin alone, a weak response is obtained. If vagal nerve stimulation and infusions of gastrin concentrations are applied together, much more acid is produced [20]. The most likely explanation of this facilitation is that vagal cholinergic activity somehow sensitizes the gastrin receptors on the parietal cells to the effect of gastrin and or that gastrin somehow facilitates sensitivity or function of cholinergic receptors [21].

This type of facilitating effect may be of general importance. Higher amounts of a hormone may be needed to induce certain types of

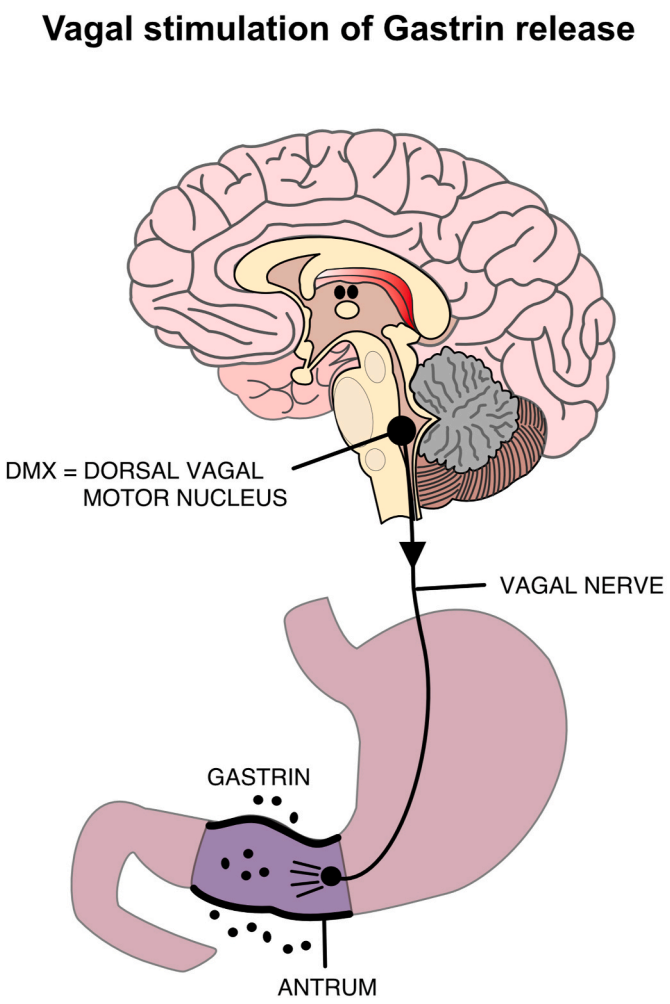

Fig. 1. The figure represents a schematic illustration of the brain and the stomach, including the antrum of the stomach, where the hormone gastrin is produced. Vagal efferent fibers originating in the dorsal vagal motor nucleus (DMX) project to antrum where they stimulated gastrin release.

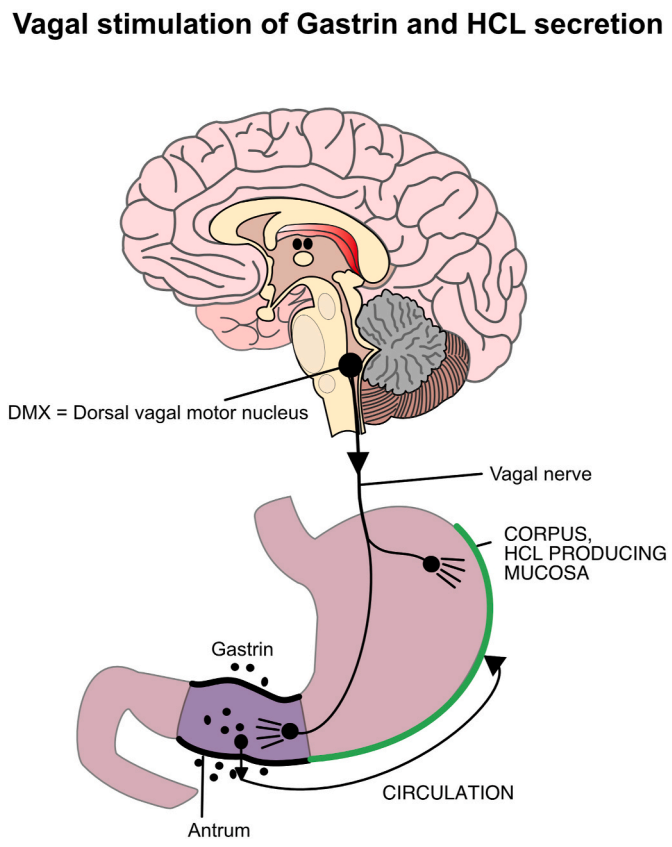

Fig. 2. The figure represents a schematic illustration of the brain and the stomach, including the antrum of the stomach, where the hormone gastrin is produced and the fundic region of the stomach, where HCL is produced in the parietal cells. Gastrin released into the circulation stimulates HCL secretion. Vagal efferent fibers originating in the dorsal vagal motor nucleus (DMX) project to the antrum where they stimulate gastrin release and to the fundus, where they stimulate HCL secretion.

physiological effects unless there is a concomitant activation of receptor function by autonomic nervous tone. Such synergistic effects will, of course, influence the dose response relationships of certain hormonal effects, as the effect size is dependent on the presence or absence of autonomic nervous tone. For example, stimulation of the parasympathetic nerves innervating the uterus increases the sensitivity of uterine muscles to the contractile effect of oxytocin. This will be discussed in more detail later.

3.1.2. *The gastric and the cephalic phase of HCl secretion*

Pavlov introduced the concept of a cephalic, vagally mediated stimulation of acid secretion. The Pavlovian tradition was kept alive at the Department of Pharmacology. A group of surgically skilled researchers were able to create pouches of the stomach in dogs. The pouches included acid secreting mucosa with or without vagal innervation and were named Pavlov and Heidenhein pouches, respectively [11,22,23]. These pouches allowed separate studies of factors that induced HCl production by local actions within the stomach (presence of food), or by central actions via the vagal nerves. Two different experimental techniques were used to induce activation of the vagal nerves in conscious dogs, sham feeding and teasing. Sham feeding allows the dogs to chew and swallow food without food entering the stomach. In this case, vagal nerve activation is caused by the stimulation of afferent sensory nerves in the mouth and pharynx in connection with feeding. During teasing, the dogs just look at and smell the food and then these stimuli trigger vagal nerve activity. Local or intragastric and central, vagally mediated stimulation of gastrin and HCl secretion are referred to as the "gastric" and "cephalic" phase of HCl secretion respectively (Fig. 3) [6].

I will never forget the profuse secretion of gastric acid juice that occurred into the vagally innervated Pavlov pouches when the dog's favorite caretaker, the pleasant and warmhearted Inga-Britta Forsman, entered the room. Obviously, the presence of Inga Britta triggered the dog's anticipation of food and, thereby, the flow of HCl via a Pavlovian conditioned reflex. I also think that Inga-Britta's caring and loving person more directly triggered the production of HCl. This experience of a strong influence on a physiological function via "cephalic stimuli" helped me later in my career to understand why social relationships and environmental cues could have such a strong impact on the physiology of wellbeing and health. It is very likely that the "Inga-Britta effect" involved oxytocinergic mechanisms. This was, however, before I knew anything about the oxytocin containing nerves that project from the paraventricular nucleus (PVN) to neurons in the dorsal vagal motor nucleus (DMX), which are involved in the control of HCl secretion. More about that later.

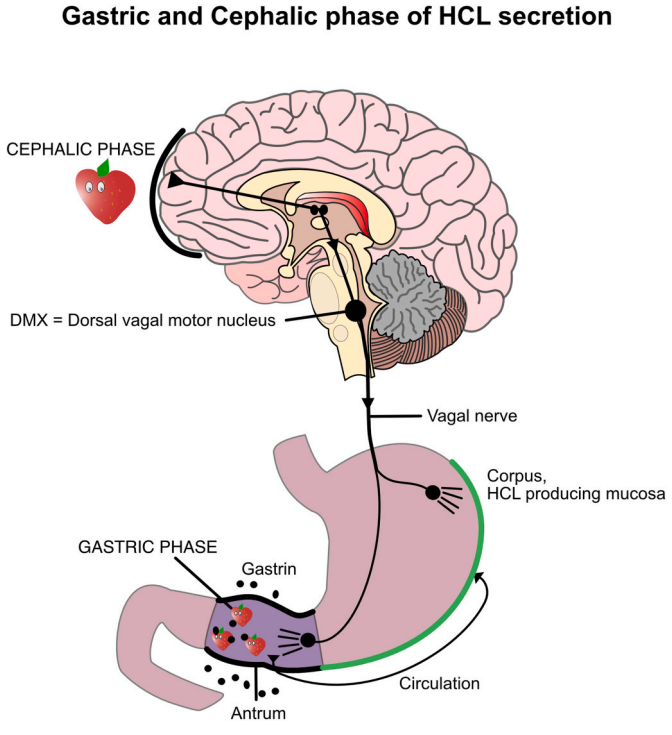

Fig. 3. The figure represents a schematic illustration of the gastric and cephalic phases of HCL secretion. The figure shows the brain and the stomach, including the antrum of the stomach, where the hormone gastrin is produced and the fundic region of the stomach, where HCL is produced in the parietal cells. Food within the antrum stimulates gastrin release (the gastric phase of HCL production). Seeing and sensing food stimulates the vagal nerves (the cephalic phase).

4. Continued research on the neuroendocrine regulation of the function of the gastrointestinal tract (1976–1980)

I enjoyed my work as a researcher, and to my surprise, I got hooked. I liked the practical, often tough work of performing animal experiments. I couldn't wait until the results, be it hormone levels determined by RIA or anything else, were obtained. I also started to enjoy writing, even if I found the language of science very formalized. I, therefore, stayed on at the Institution of Pharmacology after having defended my dissertation in 1976. I became a lecturer, which involved teaching medical students, and I continued my scientific studies regarding gastrointestinal physiology. I also received research stipends from the Medical Research Council, and I became an associate professor in pharmacology at the Karolinska Institute in 1977.

This was a fantastic time to work and perform research at the KI. The institution of pharmacology was vibrant and multiple doctoral students defended their theses almost yearly. Most of them obtained very high positions in either the pharmaceutical industry or in the government later during their professional careers unless they stayed on in their academic career. Professor *Victor Mutt* at the *Department of Chemistry* identified and sequenced new GI hormones almost every day. At the *Department of Neurobiology* Professors *Kjell Fuxe and Thomas Hökfelt* demonstrated new cells and nerves containing one or several peptides at an enormous pace. The doors were open between the different institutions and research groups, and fruitful collaborations took place all the time.

To be honest, I didn't notice any negative treatment for being a woman during my medical or PhD studies. Thirty percent of the medical students were female, and a similar proportion of the PhD students were women. It wasn't until later when I started to study female physiology and oxytocin, that I lost support and became aware of the difficulties for women in science. I will write more about this later.

4.1. *Intraluminal secretion of gastrin*

My studies on the mechanisms that control the release of gastrin continued. It had been reported that gastric juice contained a gastrin-like substance that stimulated HCl secretion [24]. Together with Professor Jens Rehfeld, I showed that the substance did indeed correspond to gastrin-17, as determined by gel chromatography [18]. A surprising finding was that much larger amounts of gastrin were released into the lumen of the stomach than into the bloodstream [25]. This was the first time I experienced "doubts" regarding my findings, and I learned that it is difficult to believe when you present unexpected results. I remember one reviewer comparing my results with the inflation of the Deutsche Mark between the First and the Second World Wars! But as mentioned above, the gastrin-like immunoreactivity had been shown to correspond to gastrin −17 [18,25].

The intraluminal secretion of gastrin occurs from a specific type of endocrine cells in the gastric antrum, which resemble taste cells. These "open" endocrine cells have an ending provided with microvilli that

project into the gastrointestinal lumen. The microvilli are provided with receptors that "sense" the presence of food constituents, intraantral pH etc. The peptides released into the lumen exert paracrine effects within the tissue of origin. In addition, they are transported downwards in the lumen of the GI tract to influence growth and function further down in the GI tract (Fig. 4) [19,25].

4.2. Sympathetic nerve activity inhibits vagally mediated gastrin release

I also investigated how sympathetic nerve activity influenced the vagally-induced gastrin release and HCl secretion together with Professor Johannes Järhult from the University of Lund. He was the expert on the physiological function of the sympatho-adrenal and sympathetic nervous system. As expected, activation of the sympathetic nervous system counteracted the vagal release of gastrin [26]. These data are consistent with the suggestion that the parasympathetic and sympathetic nervous systems antagonize each other's effects in many organs and different functional levels (Fig. 5). During physical activity eating and digestion of food is shut down - as the muscular system is in focus. This effect represents a local gastrointestinal expression of the antagonizing effect between the fight-flight system and the calm and connection system.

4.3. Somatostatin, an inhibitor of gastrointestinal and pancreatic function

At this time, it had become apparent that the peptide somatostatin, originally demonstrated to be produced in the hypothalamus and to inhibit growth hormone production from the anterior pituitary [27] was also present in endocrine cells of the pancreas and of the gastrointestinal tract [28]. Somatostatin had been shown to be produced in two different types of endocrine cells in the stomach. In the fundic region of the stomach, somatostatin was produced in classical, endocrine cells located close to the HCl producing parietal cells, whereas in the antrum, somatostatin was produced in endocrine cells of the open type, often located close to the gastrin-producing cells [19,25,28].

Somatostatin had been shown to inhibit the secretion of insulin from the pancreas [29], but the effects of somatostatin on gastrointestinal function had not yet been explored. We were able to show that infusions of somatostatin inhibit both HCl secretion from the parietal cells and gastrin secretion from the G-cells in the antrum [7,30].

In addition, we showed that the release of somatostatin was influenced by vagal nerve activity. The somatostatin release into the bloodstream decreased in response to vagal stimulation [31]. This decrease of circulating somatostatin levels may contribute to the rise of gastrin levels and the increased HCL production seen in response to vagal stimulation and suggests the presence of an ongoing inhibitory somatostatin tone. In contrast, the release of somatostatin into the antral lumen increased in response to vagal stimulation, see below [32].

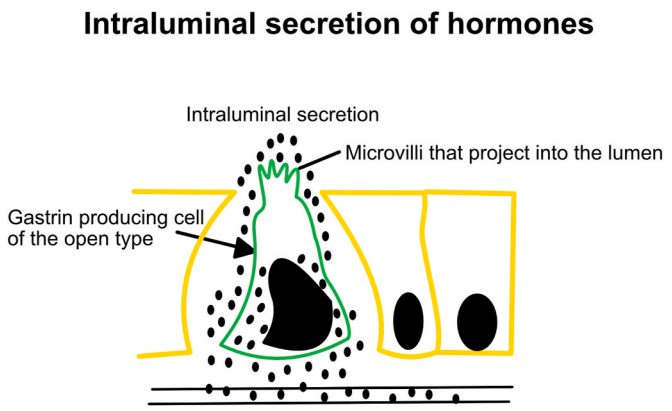

Fig. 4. A schematic picture of an open endocrine cell. The cells, have microvilli that project into the gastric lumen. The microvilli are provided with receptors that can sense different food constituents, intra antral pH etc, which influences the release of hormones. Hormones can be released into the lumen of the stomach (to exert intraluminal effects), within the mucosa (to exert paracrine effects) and into the circulation (to exert hormonal or endocrine effects). Closed endocrine cells lack contact with the lumen and hormones are released into the circulation to exert hormonal effects.

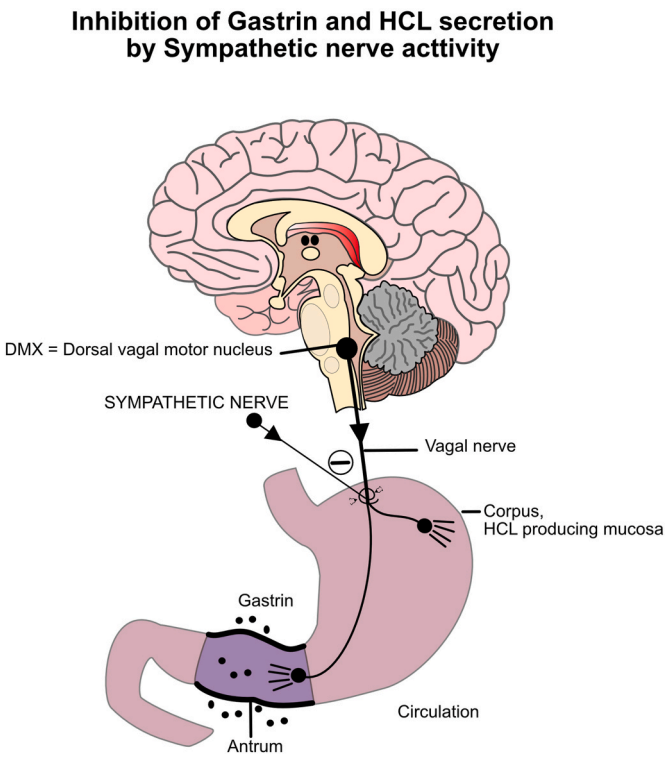

Fig. 5. The schematic figure represents how the sympathetic nerve can inhibit the activity of the vagal nerve fibers projecting to the stomach. Vagal efferent fibers originating in the dorsal vagal motor nucleus (DMX) project to the antrum where they stimulate gastrin release and to the fundus, where they stimulate HCL secretion. By inhibiting the activity in the vagal fibers, the secretion of gastrin and HCL is blocked by the sympathetic nerves.

4.3.1. Somatostatin is released by low intra antral pH

It was at this time well known that the release of gastrin and HCl secretion were inhibited at low pH in the antral part of the stomach. The inhibitory effect was suggested to be mediated by a substance released from the antrum, referred to as antral chalone, (or, if released from the duodenum, as bulbogastrone) [33]. We could show that pH inside the antrum was a key modulator of somatostatin release both into the circulation and the antral lumen [34,35]. As somatostatin inhibits gastrin release and HCl secretion [30] and as the release of somatostatin was potentiated at low antral pH [34,35], we concluded that the postulated inhibitory hormone, the antral chalone, released from the antrum at low antral pH and which inhibits gastrin release and HCL secretion, corresponded to somatostatin [33].

When the pH within the stomach, including the antrum, is low, many inhibitory mechanisms or brakes are activated to stop the production of the potentially dangerous HCL secretion. One of the mechanisms by which HCl secretion is inhibited is by stimulation of somatostatin from the antral mucosa in response to low intra-antral pH. Somatostatin, in turn, inhibits gastrin release by local paracrine mechanisms within the antrum and HCl secretion from the corpus by a hormonal action. The antral release of somatostatin in response to low pH is potentiated by the vagal nerve activity, which reinforces both stimulatory and inhibitory processes [32].

4.3.2. Link between the sympathetic nervous system and somatostatin release

Interestingly the inhibitory effect of sympathetic nerve activation on gastrin release and HCL secretion was shown to be in part mediated by a release of somatostatin. The complex interplay between vagal and sympathetic nervous stimulation, antral pH, and somatostatin release from the antrum was studied in an elegant series of experiments in collaboration with Dr Salvador Alino [36,37].

4.4. Vagal control of insulin and glucagon release

My studies on gastrointestinal function also included the vagal regulation of the pancreatic hormones insulin and glucagon. Surprisingly the characteristics of the vagal control of insulin was found to be very similar to that of gastrin. In response to vagal stimulation at 3–4 Hz a peak shaped response of insulin was induced and after 2000–3000 impulses the effect stopped and could not be reiterated until after 20 min. The vagally released insulin and glucagon was, in analogy with the vagal release of gastrin, not blocked by atropine and was therefore not mediated by a cholinergic mechanism [38,39]. In addition, sham-feeding and teasing in dogs were associated with a release of insulin and glucagon, demonstrating the importance of sensory and cephalic stimuli for the release of these hormones [40,41]. Also hormones produced in the proximal part of the small intestine are regulated by the vagal nerves (Fig. 6).

4.5. Somatostatin freezes the function of the GI tract and of the pancreas

The vagally induced release of gastrin, insulin, and glucagon was blocked by somatostatin, and somatostatin was, in addition, shown to inhibit the secretory and motor function of the GI tract as well as the function of the pancreas [7,29,30,42–47]. In this way, elevated somatostatin levels "freeze" the entire secretory and motor functions of the GI tract, including the activity of the endocrine system of the GI tract and the pancreas (see below). On the other hand, if somatostatin levels are low, GI function, including the function of the endocrine system of the GI tract, will increase, e.g., with increased digestion, anabolic metabolism, and consequently processes linked to restoration and growth. (Fig. 7).

Interestingly, circulating somatostatin levels decrease in response to feeding, suggesting that the somatostatin brake is inhibited by a vagal

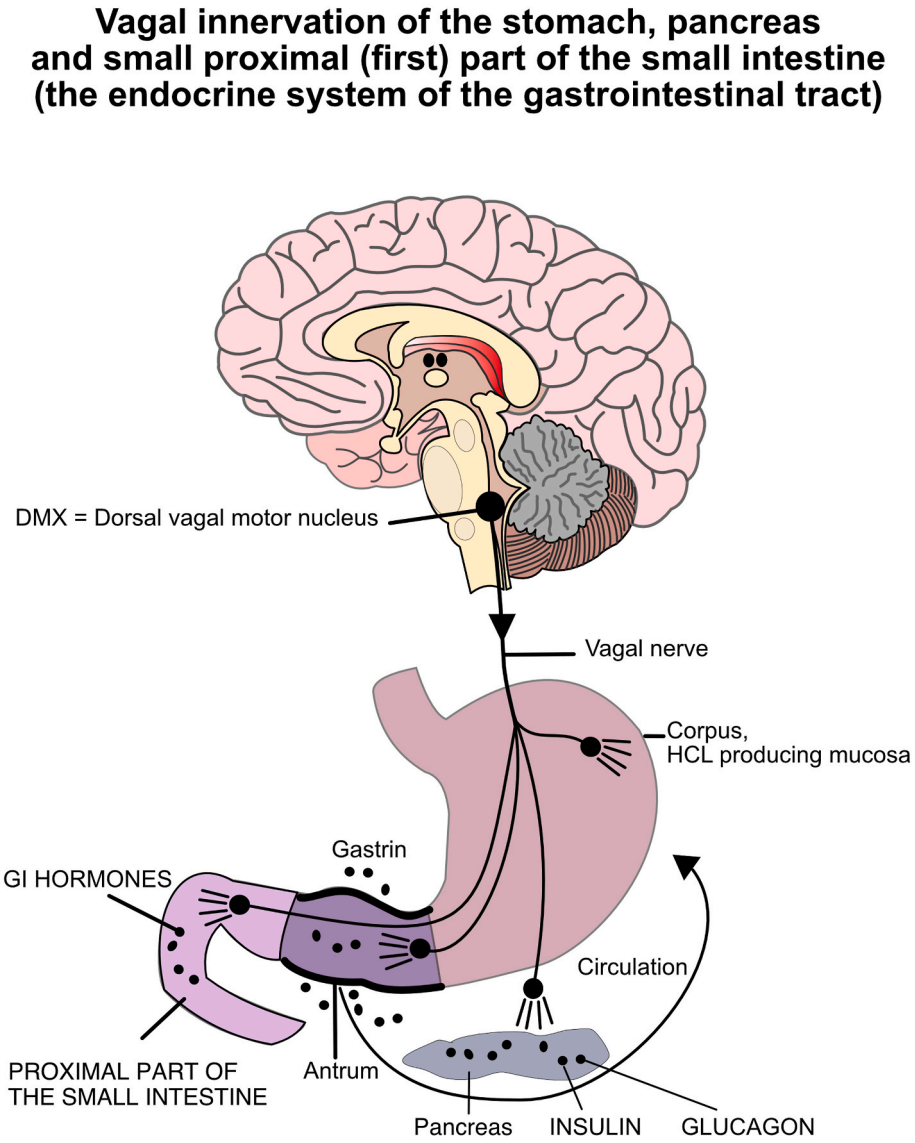

Fig. 6. The schematic figure represents the vagal innervation of the antral and fundic part of the stomach, of the proximal part of the small intestine, the duodenum, and of the pancreas. Vagal efferent fibers originating in the dorsal vagal motor nucleus (DMX) project to all these areas and thereby stimulates the function of the endocrine system of the gastrointestinal tract.

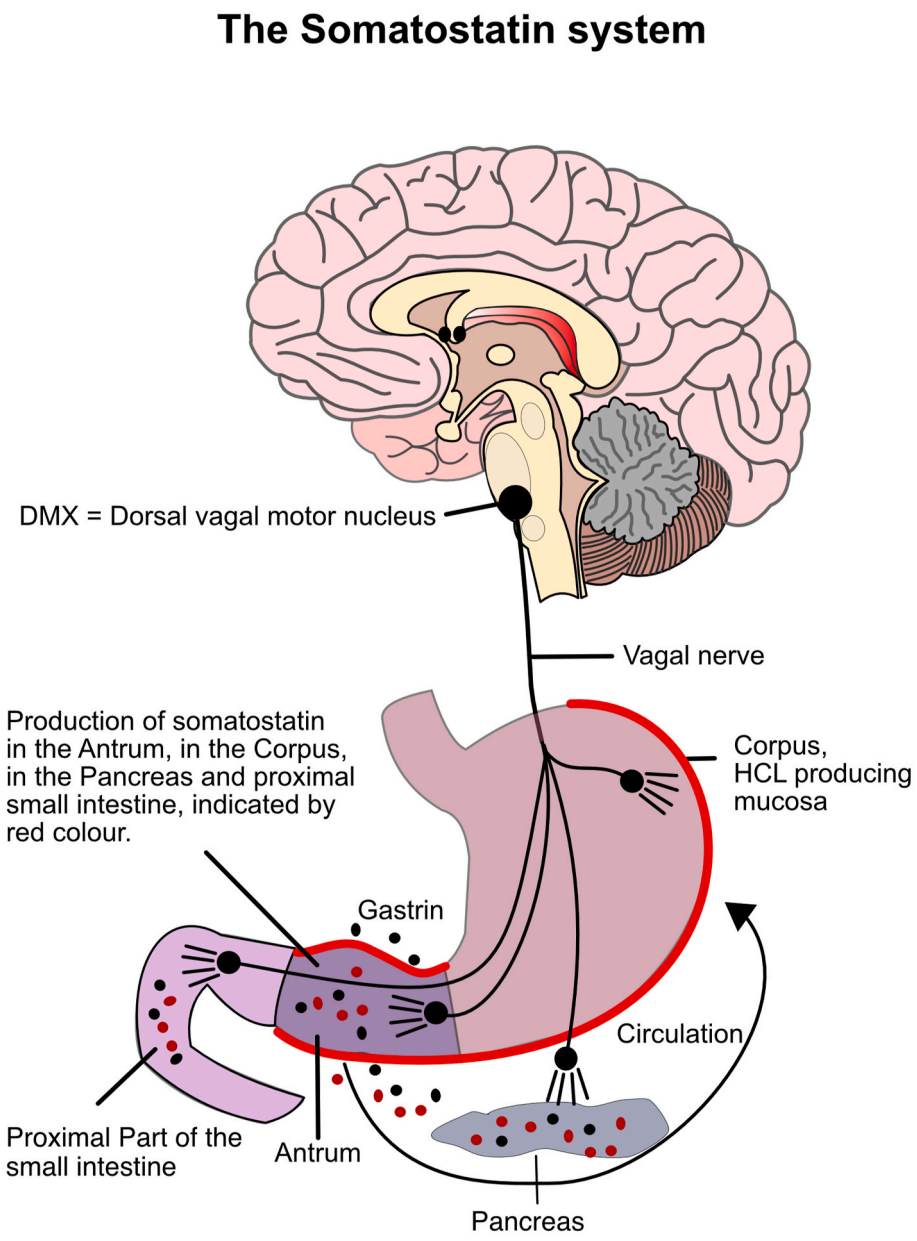

Fig. 7. The schematic figure represents the distribution of the somatostatin system. Somatostatin is present in open endocrine cells in the antral and intestinal mucosa and in closed endocrine cells in the fundic region of the stomach and in the pancreas. Somatostatin exerts inhibitory actions on other hormones produced in all these areas.

mechanism during feeding to facilitate digestive and metabolic functions [48,49]. As mentioned above, somatostatin was originally identified as the substance that inhibits the release of growth hormone, and thereby, somatostatin inhibits growth [26]. In addition, somatostatin inhibits growth by decreasing the function of the GI tract, as the GI hormones promote anabolic metabolism and growth [43].

4.5.1. Gastrointestinal peptides in nervous tissue

This was a time when peptides were shown to have multiple effects. We found that peptides like gastrin-17, insulin, somatostatin, and vasoactive intestinal polypeptide (VIP) were produced in peripheral nerves, such as the vagal and sciatic nerves. It was even possible to release these peptides in response to electrical or pharmacological stimulation of the nerves [50–55]. Gastrin - 17 was also demonstrated in the heart [56]. Vagal gastrin may be involved in the vagally mediated stimulation of gastric acid secretion as infusions of pentagastrin, a fragment of gastrin 17, inhibit gastric somatostatin release. As somatostatin inhibits HCl secretion, decreased somatostatin levels will be associated with an increased rate of HCl secretion [57]. At that time, it was suggested that the neurogenic gastrointestinal peptides exert growth-promoting effects in the innervated tissues [58,59].

4.6. The endocrine system of the GI tract

The GI tract is the site of production of many important hormones, which are involved in specific aspects of the digestive processes; gastrin stimulates HCl secretion, cholecystokinin gall bladder emptying, secretin pancreatic exocrine function, and motilin GI motility, etc. In addition, these hormones stimulate metabolic processes and participate in the regulation of food intake. These hormones together are often referred to as the *endocrine system of the GI tract*, which is, in fact, our largest endocrine system.

4.6.1. The incretin effect

Several of the GI hormones, e.g., secretin, cholecystokinin, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide −1 (GLP-1), in addition to having specific effects on the digestive process, promote insulin secretion (and sometimes also glucagon secretion) [60–62]. This insulin stimulating effect induced by GI hormones is called the *incretin* effect. Several of the incretins are under vagal nerve control, just like insulin itself. Taken together this means that food intake or feeding is associated with a reinforced release of insulin, as several mechanisms potentiate it. Insulin is released by absorbed nutrients, glucose in particular, but in addition by the direct vagal activation of the insulin producing cells which occurs in connection with food intake; in response to chewing, swallowing and even by seeing and smelling the food. Insulin release is also potentiated by the incretins released during food intake from the mucosa of the GI tract. In addition, the release of several incretins is reinforced by vagal nerve activity! No wonder extra insulin must be given in connection with intravenous glucose administration. In this case, there is no real "eating," no activation of the vagal nerves, and no release of incretins.

From another perspective, this means that food intake is not only linked to digestion but also to a strong activation of metabolic and anabolic processes, which in turn are prerequisites for restoration, growth, and even reproduction.

4.6.2. Regulation of food intake

Some GI hormones inform the CNS about the amount of ingested food and thereby contribute to regulating food intake and energy expenditure. Ghrelin, a gastric hormone that was not identified at the time that I performed my studies, stimulates food intake [63]. Other gut hormones, often produced more distally in the gut, such as cholecystokinin and glucagon-like peptides, inhibit food intake and act as *enterogastrones*.

4.6.3. Development into drugs

The extreme importance of gut hormones is reflected by the fact that several of them have been developed into pharmaceutical products. Somatostatin analogs are used to treat acromegaly and carcinoids [64], and different variants of GLP-1 are used to treat type 2 diabetes and even obesity [60–62].

4.6.4. The endocrine system of the GI tract: the basis of my future work with oxytocin

When looking back and rereading papers from my "GI period," I recall how extremely happy and enthusiastic I was during this very rewarding period of my scientific life. In connection with my exploration of my "past" scientific life, I found a small booklet that I wrote for the Swedish Associations for Physicians in 1989 called *Polypeptides in the gastrointestinal tract*. In this booklet, the structure and properties of the individual GI hormones and, in addition, how the different hormones interact with each other via local paracrine and nervous pathways effects are illustrated in simplistic figures (Fig. 8) [64].

A very integrative review of the function of the endocrine system of the GI tract is presented in this booklet. The original role of the endocrine system of the GI tract was not only to digest food; in primitive animals, it was, in addition, the source of metabolic hormones because the thyroid and the pancreas had not yet evolved. The digestive process, food intake, anabolic metabolism, and energy expenditure were all regulated by the GI tract. The endocrine system of the GI tract in mammals has retained some of these functions, which include effects on food intake and energy expenditure as well as on anabolic metabolism and growth (Fig. 9).

When I now reread this booklet, with its global, evolutionary, and psychophysiological perspective of the endocrine system of the GI tract, I realize how all the research that I performed later during my career has its roots in the knowledge that I presented in this booklet. The concepts have, of course, been extended to include reproductive processes from a

Fig. 8. The front page of the booklet *Polypeptides in the Gastrointestinal Tract*, printed by the Swedish Association for Physicians (1981).

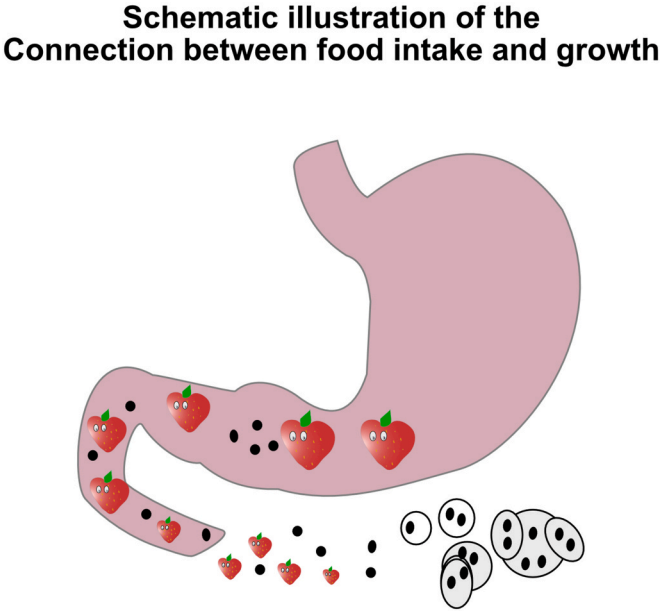

Fig. 9. A schematic illustration of the association between food intake, growth and reproduction.
From *Polypeptides in the Gastrointestinal Tract*, printed by the Swedish Association for Physicians.1981.

much larger perspective. Nervous connections between the central and the peripheral nervous system and the endocrine system of the GI tract have been identified and included in the model. From the perspective of this article, the most important extension of the model is the inclusion of the hypothalamic oxytocin system, which is linked to the endocrine system of the GI tract in a bidirectional way via the vagal nerves [65–67].

4.7. Invaluable basic methodological and pharmacological knowledge

The time spent in the Department of Pharmacology (later on Physiology and Pharmacology) has been invaluable in many other ways. I learned to perform animal experiments and obtained a deep knowledge of analytical techniques, particularly radioimmunoassay. I also learned how many pitfalls there are regarding measurements of hormone levels, including the handling of samples between collection and analysis.

When I was teaching pharmacology to the medical students, I had to learn basic pharmacology, including mechanisms of action of drugs and pharmacokinetics. I learned that lipids and peptides differ regarding their ability to penetrate biological membranes. This knowledge proved to be invaluable when I later studied oxytocin. Oxytocin, being a hydrophilic peptide, does not easily pass biological membranes like cortisol (a lipid) does. Despite this, researchers studying oxytocin often assume that oxytocin passes membranes, which leads to misinterpretations of the function of oxytocin. I also learned the difference between concentrations and amounts of a substance; I learned that volume times concentration equals amount, and I learned how to convert values between different measures, such as weight units, molar units, or biological activity. It is surprising how often these seemingly easy parameters are often incorrectly handled. My knowledge of these basic pharmacological principles has been of great help later in my scientific career, particularly when working with oxytocin.

5. A time of big changes 1980–1983

Big changes occurred in my personal life at the beginning of the 1980s. I remarried and had two more children (four altogether), which, of course, substantially increased my responsibilities and workload. I also changed my family name from Uvnäs Wallensten to Uvnäs Moberg, which I regret. I don't recommend any scientist change their family name because nobody will find or recognize the work you have done under the first name, and therefore, they don't get the full picture of your competence and achievements.

5.1. The canceled trip to USA

At the beginning of the 80s, I received a stipend from the Swedish Medical Research Council, which allowed me to spend a year in California to extend my chemical knowledge regarding gastrointestinal hormones. Everything was set; the family, including a nanny, would accompany me. Just before leaving Stockholm, I received a message that would change my view on and path of life. My research plan had been subjected to revision, and I wasn't welcome to do the postdoc any longer. Of course, I understood that the reason for their change of opinion wasn't the quality of my research plan; it was my family situation. I became extremely confused, upset, and angry. I asked myself whether women have some negative characteristics which disqualify them from doing research when they have children. Or if there were some old-fashioned discriminative mechanisms within the medical/scientific system that hindered women in their professional careers? These experiences led to a change in my research interests towards female physiology and possible psychophysiological differences between men and women, as well as to an emerging interest in questions regarding equality between men and women.

I converted my external voyage to America into an internal journey, during which I explored my experiences of motherhood, trying to translate them into scientific language. Although I gradually lost interest in the gastrointestinal tract per se, new research questions crystallized in my mind.

5.2. A new way of thinking or "seeing"

I noted that there was a change in the way I looked at things. I saw patterns and not only details. I started to include emotional experiences in addition to basic physiological mechanisms when I was writing. I sometimes found it difficult to write very formal abstracts. Instead, pictures and images became important inspirational sources for more global ideas, which ultimately resulted in research. I somehow could "see" all the effects of the oxytocin system: the inhibition of pain and stress, the activation of the GI tract, and the well-being and feeling of love and even of support in paintings, particularly religious motives. These experiences inspired experiments, and they often proved to be right, as if there is an unconscious knowledge of the distribution and function of the oxytocinergic system previously described by artists. In a way, I translated the more emotional, intuitive language of images into the more scientific and logical language of science. I started to write articles with this double perspective, e.g., an article called mod *att föda*, or *courage to give birth*, which was published in the Swedish Journal for Physicians [68]. I have described some of the basic pictures that are used in this way in the introduction to the book *Oxytocin: The Biological Guide of Motherhood* [69]. I have sometimes wondered whether this new talent had something to do with the exposure of my brain to high amounts of oxytocin during my four pregnancies and breastfeeding periods. The logical skills returned, but the new perspective remained.

5.3. The committee for equal rights between men and women (1986)

After being denied the post-doctoral position in the US (1981), I became more aware of the difficult situation for women working in science. I looked around myself, and for the first time, I noticed that the number of female researchers, in particular professors, was very low at the KI and seemed to be so also at other universities in Sweden. At this time, equal rights for women and men became a politically important issue. I was asked to create and become the chair of the first committee for equal rights between women and men at the Karolinska. I willingly agreed, and together with some other enthusiastic women, we started to find ways of helping women in their scientific careers. First, we gathered statistics about the situation of female scientists at the KI. We found that only 5 % of the professors were female, and they often seemed to be socially connected to a male professor, often working within similar fields, suggesting that female scientists at that time needed some kind of support within the system to be recognized. We tried to introduce reforms that would help the progress of females at all levels in their careers. Our suggestions were all rejected at the time but are now introduced and accepted, and the balance between women and men in leading scientific positions has become much more favorable.

An unexpected consequence of working with the committee for equal rights between men and women was that some of my own colleagues started to behave differently towards me. Instead of being treated like a nice and friendly person, I was perceived as an angry person with teeth like a wolf. I started to understand that there must be some unconscious mechanisms making people frightened of women who speak out in their own voices.

6. New research lines, based on female physiology (1981 and onwards)

During my own four pregnancies and breastfeeding periods, I had noticed some recurrent physical and emotional experiences. I had, e.g., noted that the milk ejection reflex was linked to a simultaneous feeling of thirst, which suggested that fluid intake might be increased by suckling to compensate for the loss of fluid linked to milk production and

milk ejection. It would, of course, also make physiological sense that food intake, as well as digestive and metabolic processes resulting in an optimized digestion and energy assimilation, were reinforced by suckling since this would counterbalance the energy loss of lactation. Such an effect might hypothetically be mediated via a vagally induced activation of the endocrine system of the GI tract. I found very little support in the literature for suckling-linked physiological adaptations. It was known, however, that gastrin levels in rats were elevated and that the production of gastric acid juice and the thickness of the gastric mucosa was increased during lactation, most likely as a consequence of the high gastrin levels. Together these findings suggested that the digestive capacity was increased in lactating rats [70,71].

6.1. Approached by female students when lecturing at the KI

To my joy and to a certain extent to my surprise, I was now approached by many female students when I was lecturing on the course in physiology and endocrinology at the KI. It seemed as if the concept of female reproduction and its connections with the endocrine system of the GI tract and, later on, with oxytocin fascinated and attracted them. Several female students became my PhD students, and a fantastic and productive part of my research started based on the new topic of female physiology. The scientific data that I later obtained together with some brave female pioneers (Maud Erikson, Angelica Lindén, Solveig Stock, Eva Björkstrand, Maria Petersson and Ulrika Smedh) remain an important cornerstone regarding my understanding of the oxytocin system and its afferent and efferent links to the endocrine system of the GI tract and other parts of the body. Several of them became professors.

6.2. Initiation of a collaboration with the Department of Women's health at the KI

In addition, I joined forces with one of my neighbors, the midwife Anne-Marie Widström. This was the beginning of a very fruitful and productive collaboration with midwives and pediatricians at the Department of Women's Health at the KI, which is, in fact, still ongoing. I have had the privilege of supervising the theses of all these competent midwives and physicians; Anne-Marie Widström, Eva Nissen, Anna Berit Ransjö Arvidsson, Ksenia Bystrova, Marianne Velandia, Wibke Jonas and Giovanna Marchini. In the clinical studies, we investigated the role of GI hormones and oxytocin during labor, breastfeeding, and later on skin-to-skin contact between mother and newborn immediately after birth. Thanks to this collaboration, we were able to link many clinical observations to physiological mechanisms and to interpret them from a functional and evolutionary perspective.

6.2.1. Suckling induced activation of the GI tract

A new line of research involving animal experiments and clinical studies in breastfeeding women was initiated to explore if suckling would be linked to an activation of the endocrine system of the GI tract during lactation/breastfeeding. I used the analytical and experimental knowledge that I had obtained during my previous years at the Department of Pharmacology when I studied the vagal nerve control of the endocrine system of the GI tract. We set up and developed radioimmunoassays for the determination of the levels of cholecystokinin (CCK) and vasoactive intestinal polypeptide (VIP), in addition to gastrin, insulin, glucagon, and somatostatin. Later on, we developed a highly sensitive and specific radioimmunoassay for oxytocin. We learned and developed new animal experimental models to allow studies of hormonal and neurogenic processes during pregnancy, lactation, and different types of social interaction. Often experiments were performed in collaboration with colleagues from other laboratories.

6.3. Results from animal experiments

Experiments performed in dogs and rats showed that plasma levels of several GI hormones were elevated during pregnancy. We also demonstrated that suckling in lactating animals was followed by increased levels of gastrin, insulin. and cholecystokinin and by a decrease of somatostatin [72–81]. This was the same hormonal pattern as previously demonstrated in response to electrical stimulation of the vagal nerves in cats and in response to feeding in dogs and humans. This, therefore, suggested that the suckling-induced effects on the levels of gastrointestinal hormones were mediated by the vagal nerve [6,15,16,31,48,49]. The suckling-related effect on the release of GI hormones was abolished by vagotomy, confirming that the suckling-induced effects were vagally mediated [79,81]. Taken together, our experiments demonstrated that suckling was indeed linked to an activation of the endocrine system of the GI tract and, consequently, to an enhanced anabolic metabolism. (Fig. 10).

We also found that basal levels of cholecystokinin (CCK) were lowered in lactating animals. As CCK is related to satiety (see below), these findings are consistent with a changed set point for satiety and the well-established phenomenon of lactational hyperphagia [82].

6.4. Results from breastfeeding women

The experiments performed on breastfeeding women confirmed the results obtained in the animal experiments regarding a suckling-induced activation of the endocrine system of the GI tract. Just like in the animal experiments, gastrin and insulin levels rose, and somatostatin levels decreased in connection with the onset of breastfeeding [83–87]. A similar endocrine pattern is observed after feeding in humans, i.e., a rise of gastrin and insulin levels and a decrease of somatostatin levels [48].

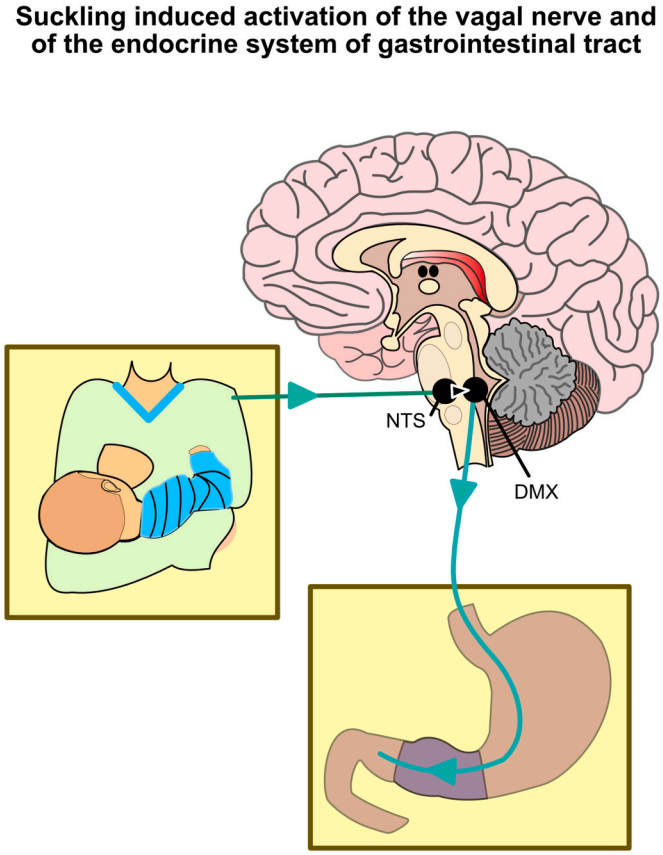

Fig. 10. A schematic illustration of suckling induced activation of the vagal nerve. The afferent nerves activated by suckling connect to the dorsal vagal motor nucleus (DMX) via the vagal sensory nucleus, nucleus tractus solitarius (NTS). In this way suckling influences the function of the endocrine system of the GI tract, to promote anabolic metabolism.

In fact, the mother "eats" from an endocrine point of view", each time she breastfeeds and, in this way, the digestive function of the stomach and the activity of the endocrine system of the GI tract will be adapted to the increased food intake needed for milk production during breastfeeding.

6.5. More milk production when somatostatin levels are low

The vagally-mediated decrease in somatostatin levels in response to breastfeeding was strongly associated with the amount of milk ejected during breastfeeding, suggesting that more milk is produced when somatostatin levels are low. This may reflect an enhanced activity of the endocrine system of the GI tract and associated increased anabolic metabolic activity as a consequence of a vagally mediated "loosening of the somatostatin brake" in response to suckling [84].

Perhaps even more intriguing was the finding that the maternal somatostatin levels obtained in connection with breastfeeding were strongly associated with the newborn's weight at birth. The lower the somatostatin levels at birth, the higher the birth weight of the newborn. This association suggests that a woman's somatostatin levels, to a certain extent, reflect her levels of metabolic anabolic activity. Low levels of somatostatin are, as mentioned above, linked to a higher activity in the endocrine system of the GI tract, which facilitates nutrient assimilation and growth and may, therefore, predict the weight of a baby at birth [85].

7. Oxytocin 1983 and onwards

7.1. The introduction to oxytocin

In the autumn of 1983, I was invited to a scientific meeting in California, which was going to deeply influence my scientific path. Around 20 scientists were invited to discuss their scientific findings for some days at a beautiful farm in California that was owned by the Kroc Foundation and funded by money from McDonalds. This meeting was one of the most rewarding experiences in my life. I presented a paper on the increased levels of gastrointestinal hormones in response to suckling/breastfeeding. During my talk, one of the participants asked a question. "Are you sure you are not measuring oxytocin?" I thought the guy was crazy because the picture that I was showing clearly indicated measurements of the gastrointestinal hormones, gastrin, insulin, and somatostatin. Then it suddenly it dawned upon me that he might be right.

At this time oxytocin was known as a female hormone involved in birth and breastfeeding. Sir Henry Dale (and some others) had demonstrated the presence of a substance in the pituitary that stimulated uterine contractions and milk ejection at the beginning of the 20th century [88]. The chemical structure of oxytocin was identified by Du Vigneaud 50 years later, which allowed synthesis and clinical use oxytocin [89]. It had also been demonstrated that oxytocin was produced in the magnocellular neurons of the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus. Then, it was transported down to the posterior pituitary, from where it was released into the circulation in a pulsatile way [90].

With the help of new histological techniques, data had started to emerge showing that oxytocin was also produced in parvocellular neurons within the PVN and that these smaller oxytocinergic nerves, as well as axon collaterals from the magnocellular neurons projected to different regulatory areas within the brain, e.g., to areas involved in the control of stress and pain and also to the vagal nuclei in the brainstem, which participate in the control of gastrointestinal function [91–93].

I suddenly understood that my colleague meant that oxytocinergic nerves projecting to the dorsal vagal motor nucleus (DMX) might be involved in the suckling related release of GI hormones that I had described in my talk. In other words, suckling not only released oxytocin from the hypothalamus into the circulation to induce milk ejection but also released oxytocin from nerves projecting to the brain stem to induce a parallel, vagally mediated release of GI hormones, which adapted the maternal physiology to the needs of lactation. From that moment on, oxytocin was included in all the experimental models and practical experiments that I worked with. I very much wish that I could remember the name of the person, who connected me to oxytocin, so that I could thank him.

8. Linking suckling to oxytocin (1983)

As soon as the oxytocin assay was developed, we included measurements of oxytocin levels in our experiments [94]. Of course, as shown before, suckling was linked to a release of oxytocin into circulation in all the animal models that we were working with: rats, dogs, sows, and cows [73,74,80,81].

8.1. Linking oxytocin to the suckling induced activation of the vagal nerve

As described above, we had shown that suckling was associated with a vagally mediated release of GI hormones [79,81]. We now additionally showed that this suckling-mediated activation of the endocrine system of the GI tract involved an oxytocinergic mechanism, as disruption of the pathways in the brain that are involved in the milk ejection reflex abolished the vagally mediated release of gut hormones induced by suckling [79]. Moreover, administration of oxytocin or an indirect release of oxytocin via the 5 HT1a receptor agonist 8-OH-DPAT was shown to give rise to a vagally mediated release of insulin as well as a decrease of the levels of somatostatin and CCK [95]. We therefore concluded that the oxytocin-mediated effect on the release of GI hormones was, at least in part, mediated by parvocellular oxytocin neurons originating in the PVN, which project to the dorsal vagal motor nucleus (DMX) in the brain stem [91–93]. These results confirmed the proposal made by my colleague at the meeting in California that oxytocin might mediate the suckling related influence on the release of GI hormones. His comment had opened up my eyes to the more overriding regulatory role of the parvocellular oxytocin neurons on basic physiological functions.

Other experimental data showed that the administration of oxytocin may, under some experimental conditions, increase food intake and also weight gain [96–98]. These data imply that oxytocin is not only involved in satiety but can also stimulate food intake in situations of extra need for calories, e.g., during lactation. In fact, the hyperphagia of lactation has been shown to involve the pathways in the brain that stimulate oxytocin release and give rise to milk ejection [99]. Part of this effect of oxytocin may be due to a vagally mediated reduction of the basal levels of cholecystokinin (CCK), as CCK is involved in food induced satiety [82].

8.2. Results from breastfeeding women

As previously shown [69,100], oxytocin levels were shown to rise in a peak-shaped way in response to suckling in breastfeeding women [101–106]. The more oxytocin released in response to breastfeeding, the more milk was ejected [101,103]. The amount of oxytocin released and the amount of milk ejected in response to breastfeeding increased over time as the infants grew and suckled more intensively (Fig. 11) [101].

8.3. Opposite relationship between oxytocin and somatostatin levels

We also demonstrated a negative relationship between oxytocin levels during breastfeeding and somatostatin levels in connection with breastfeeding [69,101,105]. The higher the oxytocin levels were in response to breastfeeding in breastfeeding women, the lower the somatostatin levels were [98], suggesting that oxytocin might inhibit the secretion of somatostatin. As mentioned above, the lower the somatostatin levels were in response to breastfeeding, the more milk was

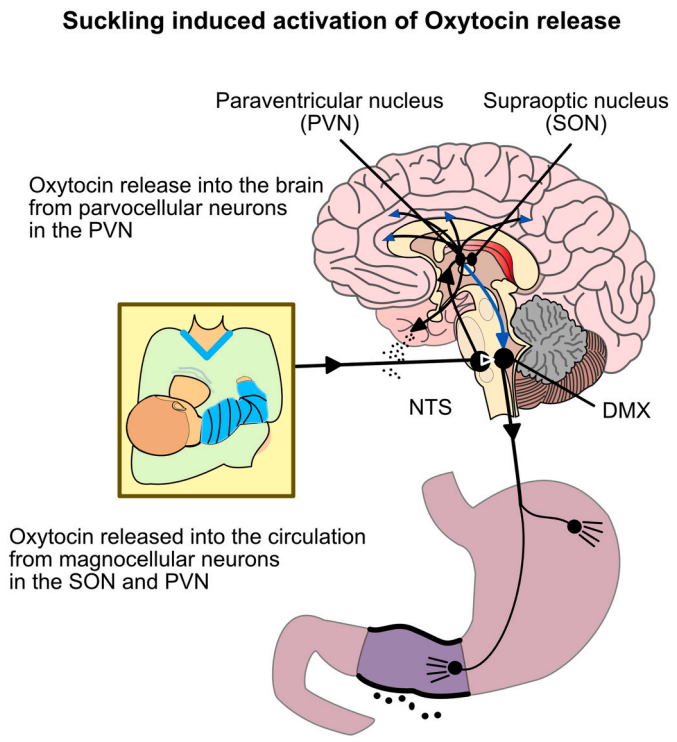

Fig. 11. A schematic illustration of suckling induced activation of the oxytocin system, via the nucleus tractus solitarius (NTS). Oxytocin is released into the circulation from the magnocellular neurons of the supraoptic and paraventricular nuclei (SON and PVN). Parvocellular oxytocinergic fibers from the paraventricular nucleus project to the dorsal vagal motor nucleus (DMX). In this way the activity of the shorter "vagal reflex" on the DMX is reinforced. In addition, parvocellular neurons are activated that project to areas involved in the control of fear, pain and stress.

ejected during that breastfeeding [100]. Taken together, these data imply that one way by which oxytocin stimulates milk production is by decreasing the activity of the inhibitory somatostatin system. In this way, oxytocin indirectly enhances the activity of the endocrine system of the GI tract, thereby optimizing the use of maternal energy for milk production. The inhibitory effect on somatostatin levels may, as suggested above, be induced by oxytocinergic fibers emanating in the PVN projecting to the DMX in the brain stem [91–93].

A negative relationship between oxytocin levels at birth and the newborn's birth weight was also established. Thus, both high oxytocin levels and low somatostatin levels were linked to higher infant birthweight [105]. This relationship may reflect the existence of tonic inhibition by oxytocin on somatostatin levels and, therefore, an increased anabolic metabolism (see above).

8.4. *Vagal activation in response to suckling, a two-step process*

We conclude that suckling, i.e., stimulation of sensory nerves originating in the nipple, induces a two-step vagally mediated activation of the endocrine system of the GI tract. The first step involves the activation of the vagal nerves via a direct connection between the sensory nerves activated by suckling and the NTS and DMX in the brainstem (Fig. 10). The second step involves a suckling-induced activation of parvocellular oxytocinergic neurons originating in the PVN, which project to the DMX, where they stimulate vagal nerve activity (Fig. 11). In this way, the oxytocinergic neurons reinforce the effect of the shorter and more direct suckling-induced reflex on vagal nerve activity and the consequent stimulation of the endocrine system of the GI tract (Figs. 10 and 11). This two-step model of suckling induced effects on the endocrine system of the GI is in line with the hierarchical arrangement of sensory reflexes involved in controlling the autonomic nervous system, as described in detail by Sato et al. [107]. A similar, two step activation of the vagal nerve and consequent activation of the endocrine system of the GI tract occurs in response to suckling in the infant (Fig. 12).

In summary, oxytocin released by suckling causes milk ejection. The milk production during breastfeeding is costly from a nutritional point of view. Women who breastfeed exclusively lose about 800 calories per day. Our data show that, at the same time, the oxytocin system via parvocellular oxytocin neurons helps the mother to handle and balance this energy expenditure. Oxytocinergic nerves adapt maternal digestion and metabolism by several vagally mediated mechanisms. It increases gastrin levels, which enhances the growth and function of the HCl producing part of the stomach. It increases the levels of insulin and of other incretins to optimize the use of ingested calories for milk production. In this way, energy expenditure is reduced, which partly compensates for the loss of calories caused by milk production/ejection [66,67]. It is possible that an oxytocin-mediated decrease in somatostatin levels is an important common mechanism behind several of these adaptive changes. In addition, oxytocin increases food intake during lactation [99]. The mechanisms behind the hyperphagia are probably multifactorial, but a decrease in basal levels of CCK is involved [82]. For a more detailed description of these events, see Uvnäs Moberg: Oxytocin, the biological guide to motherhood [69].

8.5. *Anti-stress effects of oxytocin*

Another mechanism by which energy is saved during lactation is via

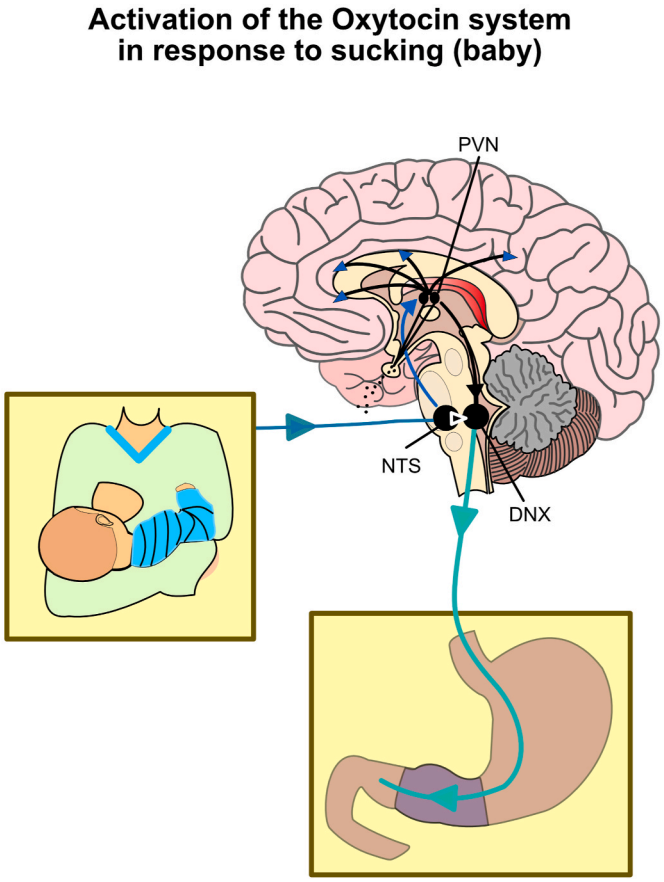

Fig. 12. A schematic picture of sucking (the baby) induced activation of the oxytocin system. Oxytocin is released from parvocellular neurons in the paraventricular nucleus (PVN) into various regulatory areas within the brain including areas involved in the regulation of vagal and sympathetic nerve function.

the profound oxytocin-mediated stress reduction that is induced by suckling. An oxytocin-mediated calming and stress-reducing effect was demonstrated by Inga Neumann and her group in lactating animals [108–110]. Further decreased levels of ACTH and cortisol in response to suckling in breastfeeding women were demonstrated by this research group [111] and others [112,113]. In our own studies, suckling in breastfeeding women was not only linked to decreased levels of ACTH and cortisol [114] but also to a substantial lowering of blood pressure. After 6 weeks of breastfeeding, basal blood pressure was decreased by 10 mm Hg [115,116].

8.6. Role of axon collaterals from the magnocellular neurons

We found a strong negative correlation between the levels of ACTH and oxytocin in blood collected during suckling in breastfeeding mothers [114]. This was unexpected since the release of oxytocin from parvocellular neurons is hardly reflected by circulating oxytocin levels. However, the correlation may be explained by the fact that the release of ACTH from the anterior pituitary is inhibited by oxytocin secreted from axon collaterals of the oxytocinergic neurons projecting to the posterior pituitary. The axon collaterals of the oxytocin neurons project to the median eminence, where the oxytocin released inhibits the release of ACTH. According to this arrangement, both the oxytocin released into the circulation from the posterior pituitary and the oxytocin released into the median eminence derive from the same neurons. This may explain why circulating levels of oxytocin are negatively associated with circulating levels of ACTH in breastfeeding women [103,114].

Taken together, these data show that suckling is not only linked to an oxytocin mediated activation of the vagal nerve with consequent activation of the endocrine system of the GI tract, but also to a simultaneous powerful anti-stress effect; a decreased activity of the HPA axis and of the sympathetic nervous system [114–116]. A low activity of the stress system and a high activity of the oxytocinergic systems is consistent with a physiological pattern of optimized growth and reproduction (Figs. 10–12). [67].

8.7. Long term health effects

These suckling-induced, oxytocin-mediated anti-stress effects may be of importance for health in the long term, as women who have breastfed have a lower risk of developing cardiovascular disease (stroke, heart infarction, and high blood pressure) in comparison to women who have not breastfed. The more children a woman has given birth to and the longer she has breastfed, the stronger the protection against cardiovascular disease [117].

8.8. Behavioral or psychological effects of breastfeeding

Breastfeeding is linked to a cluster of behavioral effects or adaptations, as mothers are adapted to motherhood during breastfeeding, and oxytocin plays a role in these adaptations [118]. In our own studies, we used the well-validated personality inventory, the Karolinska Scale of Personality (KSP). According to this, mothers become calmer, less anxious, and more socially interactive after birth and during breastfeeding [119,120].

Four days after birth, the size of the oxytocin release in response to breastfeeding was strongly associated with the mothers' assessment of these psychological variables; their levels of social interaction were positively related to the oxytocin levels and negatively with anxiety and anger and impulsivity [121]. The strong correlations between peripheral oxytocin levels and the scores of anxiety and social interaction were, in a way, surprising since central oxytocin and peripheral oxytocin levels do not always parallel each other. However, they might do so in response to suckling because (as discussed above) the magnocellular oxytocin neurons that project from the SON and PVN to the posterior pituitary are provided with axon collaterals. Such axon collaterals project to the amygdala, where oxytocin participates in the regulation of fear and social interaction [122]. It is, therefore, possible that the release of oxytocin from the axon collaterals ending in the amygdala, which gives rise to the behavioral adaptations, parallels the release of oxytocin into the circulation from the posterior pituitary since the oxytocin released derives from the same magnocellular neurons.

8.9. Lactation and maternal behavior in cows, sows, and sheep

From the beginning of the 1990s, I had some very interesting and rewarding collaborative projects with my students Bo Algers and Kerstin Svennersten at the University of Agriculture (SLU). They worked on maternal behavior and milk production and the role of oxytocin in cows and sows, respectively, and both became professors. I learned how adaptive the oxytocin effects are. The effects induced by oxytocin always help the mother/infant dyad by enhancing milk production and maternal care. However, the behaviors expressed and the mechanisms involved differ between species. It was fascinating to observe how oxytocin release in response to suckling in sows changed the frequency of maternal grunting. In this way, the sow informed the piglets about an imminent milk letdown, i.e., when food was available [123,124]. The suckling of calves gave rise to more oxytocin release in the cows than milking by traditional milking machines, suggesting that the quality of sensory stimulation during milking is of great importance for milk letdown. In addition, oxytocin was released in the calf when it was suckling the mother but not when it ingested the same amount of milk/calories from a bucket. Thus, suckling in the offspring is also linked to oxytocin release and vagal nerve activation with increased weight gain and growth [125–131].

9. Food intake influences oxytocin release via a CCK induced vagal mechanism (1984 and onwards)

Cholecystokinin (CCK) is a gastrointestinal hormone which is produced mainly in the duodenum. It stimulates the contraction of the pylorus, the gallbladder, and the exocrine and endocrine secretion from the pancreas. Efferent vagal nerve activity together with ingestion of certain food constituents, such as protein and fat trigger the release of CCK. CCK is also known to induce satiety via activation of afferent vagal nerve fibers [131].

9.1. CCK and oxytocin release

It has been known for long that afferent stimulation of the vagal nerves may induce oxytocin release and may even induce milk ejection [132,133]. In addition, CCK activates afferent vagal nerve activity and administration of CCK has been shown to give rise to increased levels of oxytocin (Fig. 13) [133].

We, therefore, wanted to investigate whether CCK might influence lactation performance via a vagal mechanism. Experiments were performed on lactating rats where the gastric and afferent vagal nerves were cut. Suckling was, as expected, associated with a release of oxytocin and prolactin. However, within a few days after vagotomy, oxytocin and prolactin release in response to suckling was completely abolished, and consequently, the pups did not receive any milk and failed to grow. Despite the inhibition of milk ejection and production, the mothers continued to overeat, and they retrieved the calories themselves [81].

This fundamental experiment indicates that both milk production and milk ejection are dependent on CCK release into the intestine and consequent activation of afferent vagal nerves. Obviously, the oxytocin-producing cells are under normal conditions and informed about the presence of nutrients in the duodenum via this CCK-activated and vagally mediated pathway. In connection with starvation, there is, of course, a lack of ingested nutrients/calories [130]. These data show that it is not the lack of calories per se that blocks oxytocin release but a lack

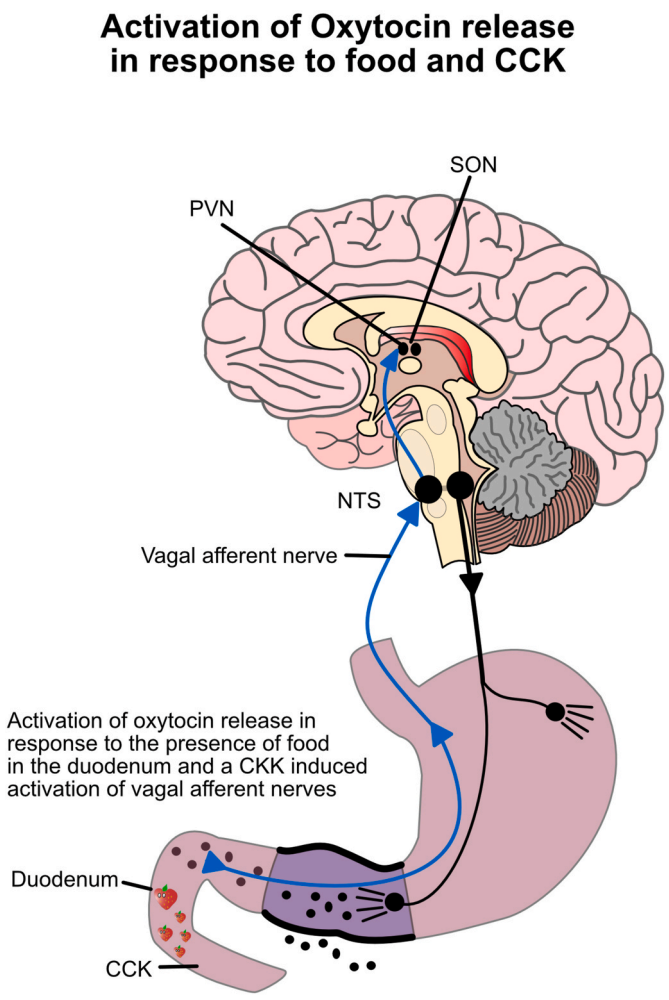

Fig. 13. A schematic picture demonstrating how cholecystokinin (CCK), released in response to the presence of food in the proximal small intestine (duodenum), activates afferent vagal nerves. After relaying in the nucleus tractus solitarius (NTS), noradrenergic neurons which activate oxytocin release from the supraoptic and the paraventricular nuclei (SON and (PVN), are triggered.

of information from the vagal afferents, which are activated by CCK. When the vagal afferent nerves were cut, the CCK-mediated information about ingested calories to the oxytocin system was lost, which the lactating dams "interpreted" as starvation. In this situation, the oxytocin levels did not rise in response to suckling, and no milk was ejected. The milk production was stopped, too, as oxytocin is necessary for the release of prolactin from the anterior pituitary [81,134].

The opposite is also true. Cows that received food during milking and in this way increased the secretion of CCK and the vagally mediated stimulation of the oxytocin system let down more milk in connection with milking than if they were not eating [131,135,136].

The maternal interaction with the pups was also inhibited by the gastric vagotomy, probably because the oxytocinergic neurons involved in maternal behavior were not activated [69]. Administration of cholecystokinin may, under certain conditions by itself, induce maternal behavior, which may be linked to stimulation of oxytocin via a vagal mechanism [137]. Also, CCK may promote bonding between ewes and their lambs. Raymond Nowak, a post-doctoral fellow from France, showed that the lambs' suckling triggered a release of cholecystokinin, both in themselves and in the ewe, which, in turn, via an afferent vagal mechanism, stimulated the release of oxytocin and, consequently, the bonding between the lamb and its mother. These studies showed that attachment or bonding involves similar mechanisms in both mother and offspring [138–140]. A similar CCK-dependent activation of other oxytocin-mediated interactive behaviors may also exist [141,142].

9.2. Cholecystokinin: the mother of the mother

Oxytocin is a maternal hormone that stimulates birth, milk ejection, and maternal caring behavior and bonding. In addition, oxytocin stimulates the growth of the fetus and milk production, e.g., by lowering somatostatin levels, thereby increasing the activity of the endocrine system of the GI tract. By modulating the activity of the oxytocin system in a calorie-dependent way via afferent vagal nerves, CCK becomes the mother of oxytocin. During food restriction or starvation, the CCK-mediated information about ingested calories to the oxytocin system is decreased, and consequently, the production and or release of oxytocin and its consequent metabolic and behavioral effects are inhibited or changed into other effect patterns, which are consistent with survival of the species. (Fig. 13).

10. Linking touching of the skin to oxytocin release and a vagally mediated activation of the endocrine system of the GI tract (1983 and onwards)

10.1. Vagally mediated connection between the skin and the endocrine system of the GI tract (1985)

When we studied the hormonal response to suckling in dogs at the beginning of the 1980s, we noticed that the dog pups, when lying together, became very sedated, and we found that the circulating levels of cholecystokinin (CCK) increased [76,77]. We assumed that the rise of CCK levels was caused by activation of cutaneous sensory nerves in response to the touch and warm temperature created by closeness within the group of pups. Therefore, experiments were performed in which the sciatic nerve was subjected to afferent electrical stimulation of low intensity. The characteristics of the stimuli were identical to those previously used to release gastrin and other hormones by efferent electrical stimulation of the vagal nerve. This type of stimulation was, at the time, supposed to reflect characteristics of transmission in nerves occurring during normal physiological conditions [14]. Stimulation of the sciatic nerve resulted in increased plasma levels of gastrin and insulin and lower levels of somatostatin, i.e., the same effect pattern as induced by efferent electrical stimulation of the vagal nerve [143]. Taken together, these data showed that stimulation of cutaneous afferent nerves activates the endocrine system of the GI tract via a vagal mechanism. In addition, a prompt and sustained decrease in blood pressure was induced by stimulation of the sciatic nerves, suggesting that sympathetic nerve activity, involved in controlling blood pressure, was also decreased [143]. (Fig. 14). The data regarding a vagally mediated release of gastrin, CCK, and somatostatin in response to stimulation of sensory afferents were later supported [144].

10.2. Connection between the skin and the oxytocin system (1988)

When the oxytocin assay was available, we also measured oxytocin levels after low-intensity, afferent electrical stimulation of the vagal and sciatic nerves. The intensities chosen were the same as those used in the previous experiments in which the release of GI hormones was studied [14]. Oxytocin levels rose in response to electrical stimulation of both the sciatic and the vagal nerves. More oxytocin was released when the frequency of the electrical stimulation was increased [94]. In addition, oxytocin levels increased after touching or stroking the legs of the anesthetized rats and also after pinching [94]. Cortisol levels had previously been shown to be released by noxious stimulation but inhibited by non-noxious stimulation [145]. Obviously, pinching is associated with a release of both oxytocin and cortisol. It is likely that oxytocin released in response to pinching serves as a buffer to the stress response. The most important information obtained from these experiments is,

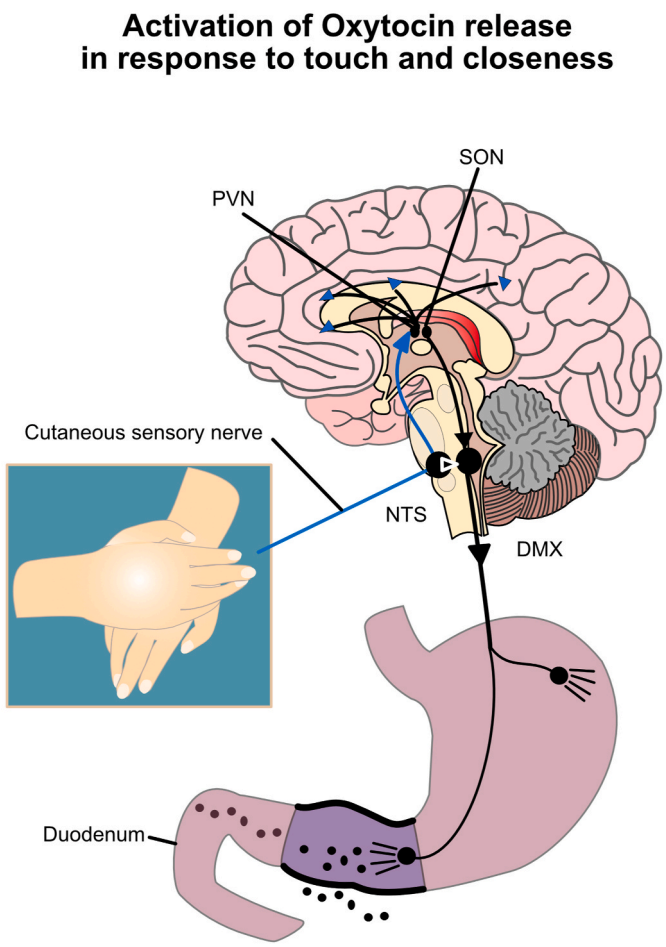

Fig. 14. A schematic illustration of how touch (activation of cutaneous afferents) activates cutaneous afferents. The sensory information reaches the oxytocin producing supraoptic (SON) and in particular the paraventricular nucleus (PVN)), via the nucleus tractus solitarius (NTS). Parvocellular oxytocin neurons are activated including fibers that project to the dorsal vagal motor nucleus (DMX). In this way the endocrine system of the GI tract is activated. Note that the effect of touching is bilateral.

however, that it is possible to release oxytocin both into the circulation and CSF in response to stimulation of peripheral nerves. In addition, the pain-relieving effect of non-noxious stimulation was shown to be in part mediated by oxytocin [146,147].

10.2.1. Unique properties of the innervation and circulation of the skin overlying the chest

The peptidergic innervation of skin overlying the chest and mammary glands was mapped using histological techniques in collaboration with Professor Thomas Hökfelt [148]. Interestingly this part of the skin was a dark spot in the histological literature. As part of this exploration, it was confirmed that there is no efferent parasympathetic innervation of the mammary gland, whereas sympathetic nerves and sensory nerves projecting to the spinal cord were demonstrated. A new finding was the demonstration of afferent sensory nerves that traveled via the afferent vagal nerve to the nodose ganglion and the NTS. Here, like other sensory parasympathetic nerves, they connect to noradrenergic fibers that in turn innervate oxytocin producing cells in the PVN and SON [69,149,150].

10.2.2. Oxytocin dilates cutaneous blood vessels and increases skin temperature

In another study we showed that infusions of oxytocin in lactating animals, in doses that induce milk let down also induce vasodilation of blood vessels in the skin overlying the mammary glands [151]. Because of the increased circulation in the skin, maternal chest skin temperature increased. In this way, oxytocin not only induces milk ejection, it also provides the newborns with warmth, which is an important function [152]. This temperature-related mechanism seems to be of utmost importance also in human mothers in connection with skin-to-skin contact after birth, which will be discussed below.

Taken together, the skin on the chest has a special innervation and also a special ability to produce, transfer and receive warmth. The specific group of vagal afferents emanating from the chest skin may be particularly sensitive to warm temperature.

10.2.2.1. The visit to Japan (1992). I met Professor Akio Sato from the Metropolitan Institute of Gerontology in Tokyo, at a conference in the US around 1990. He was an expert on the influence of stimulation of somatosensory nerves on autonomic nervous function [107]. He used an illustration of the *fight and flight* reaction during his talk, which I often use in my talks. Akio Sato used it to illustrate the activation of the stress system in response to noxious stimulation of cutaneous nerves, i.e., nerve fibers originating in the skin that give rise to stress and pain. In contrast, I used the same illustration to contrast the effect pattern induced by breastfeeding involving activation of the endocrine system of the GI tract and anti-stress effects such as a decreased activity in the HPA axis and sympathetic nervous system [69,153].

Professor Akio Sato invited me to spend a month at his lab in Tokyo in the autumn of 1992. I accepted the invitation and had a very good time, both from a scientific and social point of view, during my stay in Tokyo. I admired the high-quality science that was performed in the lab. I was very well taken care of and had great fun with the Japanese colleagues, mostly female, at this modern lab. By listening to and discussing with Akio Sato and his wife, Yuko Sato, I learned much about the autonomic nervous system and its connections to different organs and the skin. We wrote two articles together regarding the effects of stimulation of nerves from the skin and prolactin and glucagon secretion [154,155]. Mieko Kurosawa, one of the very skilled young women working at the lab in Tokyo, came to Sweden as a postdoc in my lab in 1994.

I got a clearer picture of the antagonism between the *fight and flight* pattern and the oxytocinergic *calm and connection response* and how both these reaction patterns can be triggered from the skin by noxious and non-noxious stimulation, respectively. Noxious stimulation leads to a release of corticotrophin releasing factor (CRF) in the PVN, which in turn, via separate nervous connections, activates the HPA axis and the sympathetic nervous system. The function of the HPA axis is increased in response to a CRF mediated release of ACTH from the anterior pituitary with consequent stimulation of the cortisol secretion from the adrenal cortex. The function of the sympathetic nervous system is increased via activation of CRF neurons from the PVN that project to areas involved in the control of the sympathetic nervous system. Non-noxious stimulation, on the other hand, stimulates the oxytocin system, in particular the parvocellular neurons from the PVN, which in turn activate the vagal/parasympathetic nervous system, thereby activating the endocrine system of the GI tract. Other oxytocinergic fibers project to areas involved in the control of stress, fear, and pain, where they inhibit these functions. From a functional point of view, the antagonizing systems, the CRF and the oxytocin system, also inhibit each other's functions. I have elaborated on this antagonism in more recent publications [150,156].

The cutaneous nervous pathways, consisting of only two neurons, by which oxytocin is released by touch was later described in more detail by Toku Takahashi [157]. The possibility to activate the oxytocin system by non-noxious stimulation of the skin has important clinical consequences, as it allows for specific activation of the parvocellular oxytocin neurons and their pain, fear, and stress reducing and growth-promoting effects, by touch and closeness. Such stimuli are part of manual therapies, such as massage, and may explain some of their effects [158].

10.2.3. In part, different oxytocinergic pathways are induced by suckling and touching of the skin

Suckling induces a peak-shaped release of oxytocin into the circulation, where oxytocin contracts the myoepithelial cells in the mammary gland to induce milk ejection. The circulating oxytocin originates from magnocellular neurons in the SON and PVN, which project to the posterior pituitary. In addition, oxytocin is released from axon collaterals of these neurons, which project to, e.g., the median eminence. In this way, the secretion of ACTH from the anterior pituitary is inhibited by oxytocin and, consequently, the secretion of cortisol from the adrenal cortex. Axon collaterals projecting to the amygdala may decrease the levels of fear and increase the potential for social interaction. Suckling is also associated with activating parvocellular oxytocin neurons originating in the PVN, which, e.g., increases vagal nerve activity and, thereby, the function of the endocrine system of the GI tract. Suckling is also associated with a decrease in sympathetic nerve function and, thereby, a decrease in blood pressure. The perception of pain also decreases [69,150,156].

By contrast, very little, if any, oxytocin is released into the circulation in response to stimulation of cutaneous afferent nerves, and the release pattern is never pulsatile [150,156]. Still, touch induces several oxytocin-linked effects. These effects are induced by oxytocin released from parvocellular oxytocin neurons originating in the PVN. Touching or stroking is associated with a decrease of cortisol levels without a concomitant decrease of the levels of ACTH. In this case, the decreased cortisol levels are caused by a decreased affinity of ACTH to its receptor on the adrenal cortex, which is caused by a shift in autonomic nervous tone from sympathetic to parasympathetic dominance. Also, blood pressure is decreased by a reduced sympathetic nervous tone. The function of the endocrine system of the GI tract is increased in response to an enhanced vagal nerve tone. The perception of fear and pain may be reduced, and social interaction stimulated. All these effects occur in response to activation of different components of the parvocellular oxytocinergic system [159–161] (Figs. 11, 12 and 14).

11. Closeness and suckling increase growth of infants (1983 and onwards)

At the beginning of the 1980s, a fruitful and long-lasting collaboration with Professor Jan Winberg, who was then the professor of pediatrics at the Karolinska Hospital in Stockholm, was initiated. During this period, Jan Winberg introduced me to Professor Marshall Klaus and his wife, Phyllis Klaus, who were pioneers within the field of bonding between mothers and babies, kangaroo treatment for premature babies, and support of women giving birth, "doulas." They immediately became interested in oxytocin and understood that endogenous oxytocin might be an important mediator of these effects. They visited Sweden several times and I visited them in California. A lifelong collaboration and friendship were established. Marshall Klaus was the opponent at Ksenia Bystrovas' dissertation. See below.

Based on the data from animal experiments showing that stimulation of sensory nerves from the skin increased the activity of the endocrine system of the GI tract, we postulated that touch and closeness were important for normal growth in infants. It was well known at this time that infants failed to grow and develop if they did not receive adequate amounts of social interaction and physical touch. This condition, or *failure to thrive*, was reversible and disappeared if the child received adequate amounts of social interaction. We, therefore, investigated the importance of cutaneous sensory stimulation for activation of the endocrine system of the GI tract in infants.

11.1. Small for date

In support of a deranged function in the endocrine system of the GI tract in connection with failure to thrive, we found that sick children and children who were small for date had very high levels of somatostatin [162]. As discussed above, somatostatin produced in the GI tract inhibits or freezes the metabolic function of the endocrine system of the GI tract and thereby decreases the growth potential. Somatostatin levels are increased by sympathetic nerve activity and decreased by vagal nerve activity.

11.2. Link to oxytocin

The activation of the endocrine system of the GI tract, in response to sensory stimulation of the skin, involves activation of parvocellular oxytocinergic neurons originating in the PVN that project to the DMX, as described above. Failure to thrive may be linked to reduced activation of the oxytocin system, as parvocellular oxytocinergic neurons from the PVN participate in the stimulation of the vagal nerve activity, which leads to stimulation of the endocrine system of the GI tract in part mediated by lowered levels of somatostatin. Children who do not receive adequate amounts of social interaction and touch also often, in addition to the retardation of growth, exhibit a retarded development of social skills. This deficit in social function may be another consequence of a low function in the oxytocin system, as oxytocin also promotes social interactive behaviors.

11.3. Growth promotion by sensory stimulation in infants

Skin-to-skin contact between mother or infants after birth and Kangaroo care (skin-to-skin contact with a parent) of premature infants is associated with the activation of cutaneous sensory nerves in the newborns. The pediatrician Carl Johan Törnhage performed experiments on tube-fed premature infants. The infants were receiving kangaroo care or not. In the infants receiving kangaroo care, the levels of CCK decreased under basal conditions, and they rose during tube feeding. In the control infants without kangaroo care, the levels of CCK didn't change [163]. This data showed that skin-to-skin contact induces a vagally mediated stimulation of the endocrine system of the GI tract, which may be one important factor explaining the increased growth rate observed in infants receiving kangaroo care [164].

11.4. Sucking of a pacifier stimulates growth

Sucking a pacifier also stimulates vagal nerve activity with consequent activation of the endocrine system of the GI tract. Insulin levels rose, and somatostatin levels decreased, as demonstrated by lower levels of somatostatin in gastric perfusates of newborn babies who were sucking a pacifier [165–167]. It has even been shown that bolus-fed infants increase in weight more quickly if allowed to suckle a pacifier during tube feeding [168]. These data indicate that the sensory stimulation in the oral mucosa and pharynx induced by sucking of the pacifier leads to stimulation of sensory nerves, which in turn activates the vagal nerve with consequent activation of the endocrine system of the GI tract. Bolus feeding alone lacks the cephalic phase, which is necessary for optimal digestion and growth promotion. By adding the suckling of a pacifier, the vagally mediated cephalic phase is reinstalled, and in this way, bolus feeding becomes more like normal feeding, i.e., it includes both the gastric and the cephalic phase. In several studies, suckling is associated with oxytocin release in the offspring, suggesting that parvocellular oxytocinergic neurons are involved in the suckling reflex (Fig. 12) [127].

11.5. Breastfeeding versus bottle-feeding in infants

Breastfeeding also involves more sensory stimulation in the baby than does bottle-feeding. In support of this, we found that more GI hormones were released initially during breastfeeding [169,170]. This is in part due to the fact that breastfeeding is, to a greater extent, associated with stimulation of touch receptors in the mouth and in the pharynx of the suckling infant, and often more sensory stimulation is provided

via skin-to-skin contact during breastfeeding than during bottle-feeding.

Several papers have discussed the important role of activating the endocrine system of the GI tract for growth and development. In addition, a Wennergren Symposium was organized in 1994 based on these questions [171,172].

11.5.1. Role of warmth and skin-to-skin contact after birth

Together with Ann-Marie Widström and Anna Berit Ransjö Arvidsson, I showed that when the newborn was placed in skin-to-skin contact after birth, it starts a crawling behavior to reach the mother's nipple to start suckling, a kind of "approach" behavior [173]. When the infants were in close contact with their mothers, they immediately stopped crying, indicating a calming effect of closeness or, from another perspective, that separation is linked to anxiety [174].

11.6. Rise of and pulsatile skin temperature in connection with skin-to-skin contact

The maternal chest skin is known to flush in connection with breastfeeding. The maternal breast skin temperature in connection with skin-to-skin contact immediately after birth was studied in detail in a study in St Petersburg performed together with the Russian pediatrician Ksenia Bystrova. We found that the average maternal breast temperature rose slightly during skin-to-skin contact with the newborn immediately after birth. In addition, the temperature started to pulse. The change in skin temperature is caused by an oxytocin induced vasodilatation in the skin. Both variations in circulating oxytocin levels and in changes in sympathetic nervous tone to the blood vessels in the skin contribute to the temperature variation.

The newborn responded to the maternal temperature changes by an immediate increase of skin temperature, particularly at peripheral sites, such as the feet. The more pulsatile and the greater the rise of maternal skin temperature were after birth, the more the newborn's skin temperature increased. As vasoconstriction is caused by sympathetic nerve activity, we interpreted the increased skin temperature in the newborn as an expression of stress reduction in the newborn [175,176]. In support of this assumption cortisol levels also decreased rapidly in newborns in response to skin-to-skin contact after birth [177].

11.6.1. The early sensitive period

Klaus and Kennell showed that closeness between mothers and babies immediately after birth enhanced the interaction between mother and infant for several months [178]. They therefore coined the term "the early sensitive period" for the period after birth, when long term behavioral effects can be induced. In analogy with the findings of Klaus and Kennell, we were able to show that the extra closeness between mother and newborn in connection with birth increased the duration of time the mothers spent with their newborns as well as the amount of verbal interaction between mothers and their babies during a breastfeed 5 days after birth. In addition, a vagally mediated increase in the activity of the endocrine system of the GI tract was demonstrated. The mothers also felt happier [179].

In addition, skin-to-skin contact immediately after birth was related to long-term effects in the Russian study. One year later, the interaction between mother and infant, as well as the infant's ability to handle stress, was better in the group of infants who had received skin-to-skin contact after birth than in the control group [180]. Early skin-to-skin contact was also associated with an increased weight gain per ingested calorie in bottle-fed infants, but there was no effect on the duration of breastfeeding [180–182].

Oxytocin levels rise in the maternal circulation in response to skin-to-skin contact with the newborn [106,183]. All the effects observed in mother and newborn during and after skin-to-skin contact are consistent with different aspects of the oxytocin effect pattern, the increased social interaction, the decreased stress levels, and the increased activity of the endocrine system of the GI tract. Therefore, the effects are likely to be induced by activation of the parvocellular oxytocinergic neurons of the PVN, which are activated in response to stimulation of cutaneous nerves in both mothers and newborns during skin-to-skin contact [156,159].

These data also suggest that closeness directly after birth brings the mother and newborn towards an "oxytocin-dominated state" characterized by lower stress levels and higher levels of social interaction in the short and long term. The mechanism by which the long-term effects are established is not known. It is possible that epigenetic mechanisms are activated in response to the release of oxytocin induced by skin-to-skin contact [184].

From this perspective, it is interesting that administering oxytocin to newborn rats in amounts that will allow penetration into the brain and massaging newborn rats induce a similar effect pattern (see below).

The rise of and pulsatility of maternal breast skin temperature played an important role in the immediate short-term rise of skin temperature in the newborn [176]. Also, the long-term effects were positively linked to maternal temperature. Warm maternal breast and chest skin temperature will, of course, be experienced as pleasant by the newborn. In addition, warm temperatures may send signals to the newborn regarding maternal resourcefulness. A mother with cold skin will send a completely different message to the newborn. As mentioned above, the chest is provided with a specific population of vagal nerve afferents. It is possible these vagal fibers transmit information about an increased maternal skin temperature, just as vagal afferents from the GI tract transmit information about the amount of ingested calories [156,159].

12. Basic physiological effects of oxytocin in males and females (1990 and onwards)

Maria Petersson is the doctoral student who, by far, has contributed the most to the knowledge about the basic physiological effects of oxytocin. The effects of oxytocin on the levels of GI hormones, ACTH, and cortisol, as well as blood pressure and pain threshold, were studied. The levels of GI hormones were influenced in a way consistent with increased vagal nerve activity and activation of the endocrine system of the GI tract. Blood pressure and cortisol decreased after an initial fall, and the pain threshold was increased in response to the administration of oxytocin. Repeated administration of oxytocin (1 mg/kg of oxytocin daily for five days) gave rise to long-term effects, i.e., all of the above-mentioned effects lasted for days or weeks after the last injection, often longer in females than in males. Also, the levels of glucocorticoid (GC) receptors were influenced in areas of the brain that are involved in the regulation of stress levels [185–191]. The sustained effects on blood pressure induced by oxytocin, are induced in the central nervous system (CNS), as similar effects are induced by a 1000-fold lower dose given directly into the CNS. These data are consistent with the fact that only one thousandth of a given peripheral dose of oxytocin penetrates the blood-brain barrier [187]. The repeated administration of oxytocin also decreased the levels of thyroid stimulating hormone (TSH) [192]. The influence on the levels of growth hormone (GH) was more complex [193,194].

12.1. Oxytocin stimulates the growth and relaxation response

Inga Neumann had previously shown that oxytocin administration exerts inhibitory effects on the HPA axis and that oxytocin may inhibit the activity of the HPA axis during lactation [107–109]. In our model, we demonstrated that oxytocin, in addition to inhibiting the HPA axis, exerts a broader antistress pattern as it also decreases the activity of the sympathetic nervous system and, thereby, blood pressure [195]. We also showed that oxytocin is more than an antistress hormone; it also actively induces behavioral sedation (see below), and it induces a vagally mediated stimulation of the endocrine system of the GI tract, i.e., oxytocin induces *the growth and relaxation response* [196,197]. In addition, this oxytocin regimen induced anti-inflammatory and wound healing effects [198,199]. In fact, the effect pattern resembles the

oxytocin pattern induced by suckling and other types of sensory stimulation mediated via the activation of oxytocinergic fibers emanating from the PVN [150,156,159,161].

12.2. Oxytocin and alpha-2-adrenoceptors

Several of the sustained effects induced by repeated oxytocin treatment were shown to be mediated by a changed function of alpha-2-adrenoceptors. This was demonstrated using classical pharmacologic experiments, as alpha-2- receptor antagonists abolished the lowering of blood pressure and pulse rate induced by oxytocin [200]. Oxytocin treatment also decreased the firing of single noradrenergic neurons within the Locus Coeruleus (LC), an important site for the regulation of stress [201]. In addition, oxytocin was found to increase the expression of alpha-2-adrenoceptors in areas involved in the control of autonomic nervous tone [202,203]. The alpha-2- adrenoreceptor system has been labeled the "energy conservation system," i.e., it is a system that facilitates storing of nutrients and, thereby, healing and growth. This effect pattern is similar to the oxytocin-induced activation of the *growth and relaxation response or the calm and connection response*.

The long-term increase in pain threshold, induced by repeated injections of oxytocin, was mediated by the increased function of opioidergic mechanisms involved in the regulation of pain threshold [186].

12.3. Is oxytocin degraded to several active oxytocin metabolites?

It is possible that the powerful long-term effects of oxytocin, requiring high doses of oxytocin, are induced by an active oxytocin metabolite, which is produced by enzymatic degradation of the non-apeptide oxytocin after some delay. This idea is supported by the fact that administration of peptidase inhibitors before oxytocin treatment, blocked the development of an oxytocin mediated decrease of blood pressure [204]. When the effect of different fragments of oxytocin were studied, fragments containing the C – terminal part of oxytocin, were linked to the antistress and sedative effects of oxytocin, whereas the whole molecule or fragments from the mid region of oxytocin were associated with the exploring and anxiolytic effect of oxytocin [204].

12.4. Different effects of oxytocin in familiar and unfamiliar surroundings

It is well known that some oxytocin-mediated effects are modified by the environment. If a rat mother feels that her offspring are threatened, the oxytocin mediated maternal caring behavior will be converted into a defensive behavior, maternal aggression [110]. In the experiments performed by us to demonstrate the long-term antistress effects of oxytocin, the environment was shown to influence the effects of oxytocin. In animals that were subjected to repeated treatment of oxytocin calming and antistress effects were normally observed in a familiar environment. If, however, animals were moved to a non-familiar place, stress effects, such as elevations of blood pressure were observed [205]. These data show that not only oxytocin induced behavioral effects, but also physiological effects are dependent on environmental cues.

12.4.1. Oxytocin administration to newborn rats gives rise to lifelong effects

If the repeated oxytocin treatment regimen was administered to newborn rat pups, the effects became more striking, as they were lifelong. Not only did the adult animals that had been treated with oxytocin when newborn, have lower blood pressure and cortisol levels, as well as higher levels of GI hormones than controls, the expression of alpha-2-adrenoceptors was also significantly enhanced. In addition, their pain threshold was elevated [98,206–208].

12.5. Reversal of effects caused by stress during pregnancy

Oxytocin administration to newborn pups even reversed elevated stress levels induced by maternal stress during pregnancy. The elevated blood pressure and cortisol levels in adult rats born to mothers exposed to food restriction during pregnancy, were reversed if the pups received oxytocin post-partum Annika Sohlström, a post-doctoral student and an expert on nutrition, contributed with her knowledge and expertise in these experiments [209–212].

Food restriction is a stressor to the mother, that is "transferred" to the offspring during pregnancy. Perhaps a reduction of maternal CCK release, due to the restricted food intake, is one of the factors behind the increased stress levels in the offspring. Perhaps a reduced input to the maternal oxytocin system, via the CCK activated vagal afferents, changes the way by which the mother handles, or partitions energy. As less food is ingested, she invests less calories in the offspring.

These results, in addition, indicate that there seems to be a period, or a biological window, after birth, when administration of oxytocin has the potential to induce long term, even life long, effects and even reverse stress effects induced during pregnancy. This finding is of clinical importance as similar effects are obtained in response to closeness between mother and infant immediately after birth, i.e., oxytocin levels rise and consequently stress levels are reduced and effects related to anabolic metabolism and growth are enhanced, see above. As also presented above, the effects of skin-to-skin contact immediately after birth, i.e., during the early sensitive period, become long-lasting [173,178,180].

12.6. Administration of oxytocin during pregnancy

Oxytocin administration to pregnant dams, with free access to food, increased the weight of the placenta and the number of fetuses. If the oxytocin treated dams were additionally subjected to food restriction, the placental weight and the number of fetuses were reduced versus controls. The individual fetus, however, weighed more [213]. Together these experiments show the intelligence of oxytocin in the sense that its effects are dependent on or modified by the environment, e.g., by the availability of food in a way that is consistent with an optimized chance of survival for the offspring. Plenty of food is linked to creation of many pups, whereas the mother gives birth to fewer pups, if subjected to food restriction during pregnancy, which will of course facilitate providing of the pups with food and care later on, It is likely that activation of the maternal CCK system and consequent activation of the oxytocin release "informs" the mother regarding the availability of calories, just as during lactation, so that the correct strategy for the use of energy is chosen.

12.7. Oxytocin increases the growth and reproduction of plants

As oxytocin stimulates growth in mammals, I wondered if it would exert similar effects on plants. I made some experiments with cress seeds in my kitchen. I added different amounts of oxytocin, when I watered the cress and obtained a beautiful dose response curve. Many other plants grow more quickly and become bigger if oxytocin is added. These effects of oxytocin point to a very old mechanism of action, which is shared by plants and animals. These findings were patented.

12.7.1. The calming massage by Dr. Kanetake (1992)

During my stay in Tokyo, I learnt a massage technique from Dr. Kanetake by which rats, became sedated and insensitive to pain within minutes, if firmly stroked on the ventral side of the chest. This technique was sometimes used for short term anesthesia of the animals during surgical procedures at the lab in Tokyo. I was intrigued by the results of this type of massage, as the effects were very similar to the ones induced by suckling and by the evolving data regarding effects following administration of oxytocin. So back in Sweden, a series of studies were initiated to study the physiological effect profile of "the Kanetake type of

massage". The massage was shown to induce sedation, increase pain threshold, increase the activity of the endocrine system of the GI tract and to lower blood pressure and heart rate. In addition, it increased the levels of oxytocin [214–219]. The pattern of physiological effects was identical to the pattern of effects observed in response to repeated administration of oxytocin (see below). If the massage treatment was repeated, effects became long-lasting like the effects of repeated oxytocin administration [216].

As described above there is a special vagal afferent connection between the skin overlying the chest and the SON and PVN. It is possible that the firm sensory stimulation of the skin induced by the Kanetake type of massage, activated oxytocin release from parvocellular oxytocin neurons, to induce oxytocin effects.

12.7.2. Life-long effects of massage given to newborn rat pups

Experiments were also performed in which massage was given to newborn rats. Similar effects, as in the adult animals, including lowering of blood pressure was induced. In addition, the effects remained into adulthood [206]. These data are consistent with previously published data showing that additional sensory stimulation of the skin in newborn animals induces stimulation of growth and decreases stress levels [220]. They are also consistent with the studies performed by Meaney, Champagne et al. [221,222] showing that extra maternal licking of rat pups gives rise to decreased levels of anxiety, decreased activity of the HPA axis and increased social interaction in adulthood. These effects, among others, involve an increased function of oxytocin receptors in the amygdala, a general decrease of stress levels including an increased activity of alpha-2-adrenoceptors might be involved.

It is possible that pheromones participate in the effects caused by massage. Administration of oxytocin to rats is followed by secretion of a pheromone from the treated rats that stimulates oxytocin secretion and oxytocin effects, such as stress reduction and elevated pain thresholds, in neighboring rats [223,224].

12.7.3. Behavioral and pharmacological effects of oxytocin (1992)

In the beginning of the 1990s, Professor Sven Ahlenius came to the department of Physiology and Pharmacology. He was an expert on behavioral psychopharmacology and was associated with the CNS division of Astra Zeneca. His former doctoral student, Viveka Hillegaart, became a post-doctoral fellow in my lab. The three of us joined forces to perform a lot of studies together and became very good friends. Unfortunately, Sven Ahlenius unexpectedly died in 2001. We performed interesting experiments showing that, oxytocin has two, in part, opposite effects on behavior. A low dose of oxytocin (1 ng/kg) given intracerebroventricularly gave rise to an anxiolytic and activating effect, whereas a high dose oxytocin (1 μg/kg) induced a sedative, calming effect. One-thousand-fold higher doses were needed to induce these effects by subcutaneous administration [225–227]. The high dose of oxytocin was also associated with improved conditioned avoidance learning [228].

12.8. Two behavioral effects of oxytocin during social interaction

Hypothetically both these effects could be involved in social interaction; the low dose, anxiolytic effect of oxytocin could be linked to initiation of social behavior or approach of another individual whereas the second high dose, sedative effect of oxytocin might be linked to the antistress and growth promoting effects in response to activation of cutaneous afferent nerves during social interaction.

The high dose effect pattern could correspond to the effects induced by the *Kanetake type* of sensory cutaneous stimulation, which was shown to give rise to sedation, antistress and growth promoting effects. From a pharmacological point of view this effect should be related to the oxytocin-induced activation of alpha-2-adrenoreceptors as administration of oxytocin in the higher dose range gives rise to not only sedation, but also antistress and growth promoting effects, which seem to be linked to an increased function of alpha-2- adrenoceptors.

Such a sequential release of oxytocin was later demonstrated in connection with interaction between humans and dogs. After a short period of separation, seeing and approaching of the owner was linked to a short peak-shaped release of oxytocin in the dogs. Consequent stroking together with verbal interaction with the dog was associated with a sustained rise of the dog's oxytocin levels and the dogs calmed down. In the absence of the expected positive interaction from the owner, there was no second phase of oxytocin release, rather a decrease of oxytocin levels and a rise of cortisol levels. In addition, the animals became very distressed [229].

12.9. Oxytocin and serotonin

To investigate whether some of the behavioral effects of oxytocin were linked to serotoninergic activity, the oxytocin releasing effect of different types of serotonin receptor agonists were investigated. We found that 5 HT-1A receptor agonists, had the strongest effect on oxytocin release [230].

12.10. 5HT and the gastrointestinal tract

As discussed above, oxytocin exerts a multitude of effects on food intake and metabolic variables which depend on the internal and environmental conditions and on demands. One interesting finding was that administration of a 5 HT 1A agonist, 8-hydroxydepat, increased insulin levels and decreased the levels of somatostatin and cholecystokinin via an oxytocin mediated vagal pathway [97]. This effect is activated by suckling during lactation to increase food intake and maximize the use of calories to compensate for the loss of calories via milk production as discussed above.

Activation of such a physiological pathway, associated with enhanced food intake and nutrient assimilation, can exist also in non-lactating individuals. Interestingly, in a collaboration with Professor Carl Otto Jonsson from the department of Psychology of Stockholm University, we found a strong correlation between high insulin and low levels of cholecystokinin and body mass index (BMI) in a sample of grossly overweight people (data not published). This suggests that one way by which overweight people obtain and retain their adipose tissue, might be an overactivity in the vagal efferent nerves, which decreases somatostatin levels and raises insulin levels, thereby potentiating the storage of nutrients and, in addition, decreases the CCK levels, thereby increasing food intake.

12.11. SSRI and oxytocin

In early studies, the effect of serotonin uptake inhibitors (SSRIs) on oxytocin release was investigated These drugs induced a substantial rise of oxytocin levels suggesting that a release of endogenous oxytocin could be part of their mechanism of action [231]. Clinical studies later supported the assumption that oxytocin may be involved in some of the anxiety-relieving effects induced by SSRIs [232]. Amperozide, an antipsychotic, also released oxytocin, suggesting that endogenous oxytocin may take part in some of the effects caused by this drug [233].

12.11.1. Patent applications

In the late 1990s, researchers at the KI were encouraged to patent their results and to be part of companies in which inventions were to be developed and commercialized. Together with KI, patent applications, regarding the role of oxytocin in wound healing, pain relief and attraction to odors were made. These applications were then moved to a company called Entretech Medical and further patent oxytocin applications, e.g., wellbeing, lowering of blood pressure, menopausal disorders, growth of plants etc. were filed. "A male research colleague", who had participated in some of the experiments on which the patent applications were based, was a co-inventor of several of the patent

applications.

13. Oxytocin may mediate wellbeing and health induced by social interaction

In the 1990s, it was well known that positive social interactions between humans are linked to better health, in particular cardiovascular health [234]. Based on the results from my experiments performed on animals, which were supported by studies performed on mothers and their infants, it was obvious that stimulation of sensory nerves from the skin was linked to activation of parvocellular oxytocin neurons. Oxytocin neurons projecting to the DMX stimulated digestion and the activity of the endocrine system of the GI tract and, thereby, anabolic metabolism and growth via a vagal mechanism. In addition, stress levels were reduced via oxytocinergic neurons, with decreased activity in HPA axis and in the sympathetic nervous system. In addition, sedation was induced.

The same effects could be induced by administration of oxytocin and these effects became sustained following repeated administration of oxytocin. As oxytocin has been shown to be released by stimulation of cutaneous nerves, together these data indicate that oxytocin can mediate the effects of touch and closeness, (Fig. 14).

The results, cited above, showing that administration of oxytocin or of different types of sensory stimulation of the skin was linked to oxytocin release, were associated with the calm and connection or growth and relaxation response, indicated that social interaction should involve this oxytocin linked effect spectrum, as social interaction involves touch and other types of physical interaction. Social interaction should therefore not only reduce stress levels as previously shown, but also increase the activity in the endocrine system of the GI tract and therefore be health promoting in a broader sense [235,236]. Obviously interaction at the psychological level could contribute to the effects on mental and physical health [237] (Fig. 14).

The failure to thrive syndrome in infants, with its retarded growth and high levels of somatostatin, as described above, is the result of lack of social interaction. Deficits in social interaction occur in adults too, and social isolation is linked to an increased risk of depression, anxiety, and cardiovascular disease [238].

Oxytocin has not yet been used as a pharmaceutical drug to promote health but could be in the future. The hyperinflammation of covid could e.g., be treated with oxytocin, with its potent anti-inflammatory effects [239–242].

13.1. Sue Carter and Stephen Porges

Somewhere in the beginning of the 1990s I met the oxytocin lady of the US, Professor Sue Carter and her husband, Professor Stephen Porges. Sue Carter had performed important studies regarding the role of oxytocin and vasopressin on pair bonding and other types of social interaction in voles [243]. Her husband, Stephen Porges, was working on his extremely interesting polyvagal theory. I remember that I found it curious that he didn't include oxytocin in his concepts [244]. Since I had worked with oxytocin-linked physiological and psychological effects in response to sensory stimulation of the skin, which is a fundamental part of social interaction, the three of us had a lot in common. The discussions were endless. We became great friends, and I visited Sue and Steve several times in their generous home in Bethesda, where they introduced me to different aspects of US society. I am so grateful for this introduction to the American culture and society.

13.1.1. The Wennergren symposium, "is there a neuroendocrinology of love?"

Since we were all interested in oxytocin and social relationships, Sue Carter and I organized a Wennergren symposium in Stockholm 1996, which was named, "Is there a neurobiology of love". This meeting was the first one on this subject and became a great success. We succeeded in gathering many prominent scientists from the field for the meeting. Sue and I wrote an introduction to the conference proceedings, which were published in Psychoneuroendocrinology in 1998 [245].

13.1.2. The NIH application

In my lab, we had, as described above, made some very interesting experiments, showing that postnatal administration of oxytocin to rat pups for five days induced lifelong effects, including anti-stress effects [98,206–208,210–212]. Sue Carter was interested in investigating whether the 5-day postnatal oxytocin treatment would also influence the behavior of the adult rats. We, therefore, together applied for and received an NIH grant regarding morphological changes in the brain and physiological and behavioral long-term effects of oxytocin administration to newborn rat pups. My role was to continue the investigations of postnatal oxytocin treatment on physiological variables. Sue Carter was the principal investigator of the project. The NIH application ended in 2000.

Sue, Steve, and I spent, thanks to Sue's administrative efforts and skills, the summer of 2000 at the Rockefeller Center in Bellagio, located close to the lake of Como, in Italy. A new period of endless stimulating discussions and interactions with researchers from other scientific fields took place.

14. Adversities and difficulties (1994 and onwards)

14.1. Applications for professorships

The first professorship I applied for was a position in Physiology at the KI in 1992. My research program was based on oxytocin and its effects on behavior and physiology. I was one of the top candidates, and recommendations regarding equality between women and men were raised. In connection with this process, two professors at the department of Physiology and Pharmacology wrote an article against my candidature in one of Sweden's most read daily newspapers (Dagens Nyheter) in 1994 [246].

Soon thereafter, the government created a few special professorships for women who worked with female research subjects to help them in their careers. In 1995, the KI applied for three and received two of these professorships, one of which was based on my oxytocin research. When the KI announced the position based on my oxytocin research it was no longer linked to oxytocin research. The position was given to a younger and, from a research point of view, less experienced female colleague working with diabetes. One of the reviewing experts was a professor from the Department of Physiology and Pharmacology who ranked me very low in contrast to the two other external reviewers, and the question of conflict of interest was raised [247].

14.2. Other difficulties

Many other difficult and damaging things happened during the late 1990s, with a peak in 2000–2001. I was asked to change labs twice within the Department of Pharmacology and asked to break my collaboration with Prof. Sven Ahlenius. Doctoral and ethical applications, scientific data, articles, and patent and research applications were copied or slightly rewritten and taken over by another person.

I tried to make my voice heard and explain what was going on. I compiled material and wrote summaries to the ethical committee of the KI and other institutions of what had happened, but nobody was interested. I was accused of being a difficult person who was problematic to work with.

Several KI researchers initiated an investigation by the ethical committee in 2002 [248] and a more extensive investigation by the Swedish Medical Research Council took place in 2003-4. A "colleague" was found not to have followed good scientific practice (2006) [249] and was no longer allowed to perform research at the KI (2007) [250].

In 2018, I was urged to submit an application for a European Co-

operation in Science and Technology (COST) Action from the European Union. I asked the director of the KI if I could do this from the KI, and I sent him a summary of my research experiences at the KI. As nothing happened, I recently asked to get the summary back, but it could not be found [251].

14.3. Possible reasons for the difficulties

I sometimes wonder why I have had to face so many, from my perspective, unfair difficulties.

Did I become a female scientist at the wrong time? Did I lack support? Did I evoke resistance in the medical establishment by actively working for equality between men and women? Did I evoke resistance by working with a nonclassical research subject, such as female physiology? Did I obtain scientific results that others envied and wanted? Did I become a victim of the modern fusion between academia and the pharmaceutical industry with its unclear borderlines between the classical academic type of science performed at university institutions and the research performed by the pharmaceutical industry with its drive to obtain quick financial rewards? There were rumors about a commercial agreement, but it was never shown to me. Or did I have bad luck or "bad karma" because of an "unfortunate position of the" stars when I was born?

In retrospect, I can see how unfortunate it was that an article against my candidature for a professorship was published in a daily newspaper in 1994 [246]. How easily individuals follow each other's behavior! Everything would have been different if the leadership of the KI had distanced itself from this article.

15. Moving to the Swedish University of Agriculture in Uppsala (SLU)

I obtained a professorship in physiology at the Department of Animal Physiology at the Swedish University of Agriculture in Uppsala (SLU). I gradually started to move there around 2000. To me, this was a difficult and frustrating experience. I had long collaborated with wonderful colleagues at SLU in research projects regarding lactation and interaction between mother and offspring and continued to do so. However, since there were no facilities for experimental research on rats, I could not perform exploratory physiological experiments to continue my studies on oxytocin.

15.1. Human–animal interaction (2002)

At this time, the scientific literature convincingly showed that interaction with pet animals increased health and well-being for their owners. Having a dog was, for example, associated with lower blood pressure, lower stress levels, and fewer doctor visits. Elderly people got less depressed if visited by dogs, and the symptoms of children with autistic problems decreased with the help of an animal pet [252].

I immediately saw the similarity between this effect spectrum, consisting of stress reduction, healing effects, and increased social interaction, and the effect pattern caused by positive relationships between humans. In addition, I saw that this effects spectrum corresponded to different aspects of the oxytocin-related effect pattern. I, of course, knew, as presented above, that interaction between mothers and their newborns after birth is associated with decreased levels of anxiety, anti-stress effects, such as lowering of pulse rate and cortisol levels, anti-inflammatory effects, growth-promoting effects, and enhanced social contact between mother and infant. These effects were suggested to be mediated by the oxytocin system, which was activated by touch and other sensory stimuli during the interaction between mother and infant.

Therefore, we wanted to show that interaction between humans and their pets is also linked to oxytocin release, as this would support the hypothesis that endogenous oxytocin may also mediate the health-promoting effects during human animal interaction. Together with Linda Handlin, an experimental series was performed to study the effect on oxytocin levels. in both the owner and pet, caused by the owner's stroking and caressing of the dog. The results showed that oxytocin was released in both owners and dogs. Interestingly, the oxytocin release in the owners and their dogs was synchronized; the higher the oxytocin levels in the owners, the higher the oxytocin levels in the pet! In addition, the more the owner liked her dog, the more oxytocin was released in both the owner and the dog (Fig. 15)! [253–256].

In another experimental setting, Linda Handlin and Anne Nilsson showed that regular visits by dogs at a nursing home for older people lowered the resident's blood pressure and heart rate and increased finger temperature, a sign of well-being and relaxation, for weeks after the last visit by the dog. The effect on blood pressure was like that caused by pharmaceutical drugs, suggesting that dogs might, to a certain extent, substitute for pharmaceutical drugs in the elderly [257].

15.1.1. The German-Austrian collaboration

At this time, I had the privilege of meeting some other European researchers who were also interested in the effects caused by interaction between humans and animals: Professor Henri Julius, Dr Andrea Beetz from Germany, and Professor Kurt Kotrschaal, who was at the time head of the Konrad Lorenz Institute in Austria. We decided to write a book on how interaction/attachment with pets influences human health from an

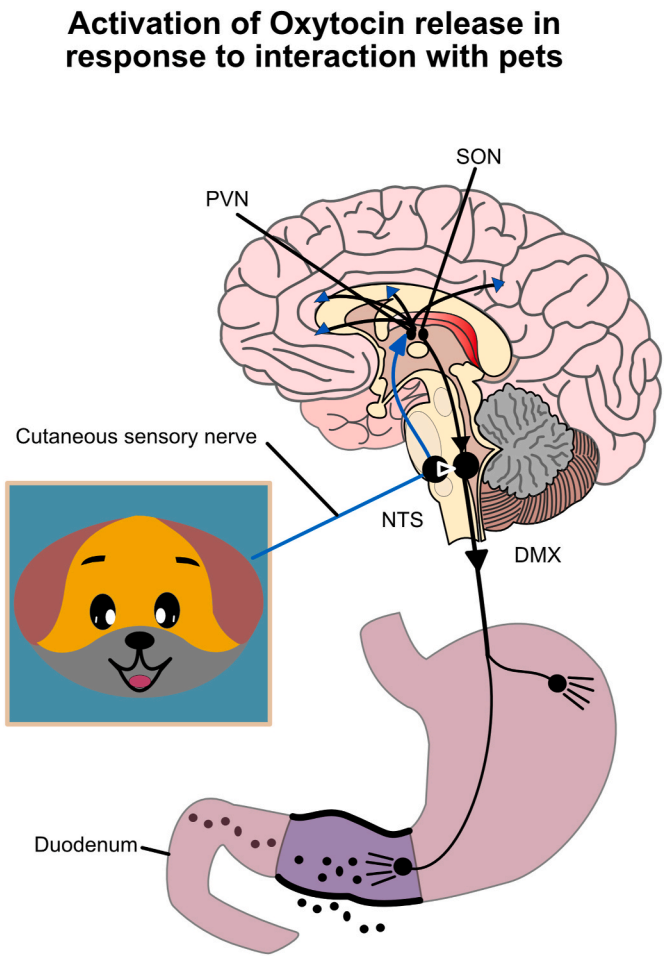

Fig. 15. A schematic illustration of how physical interaction with a dog (or other types of pets) activates cutaneous afferents. The sensory information reaches the oxytocin producing supraoptic (SON) and in particular the paraventricular nucleus (PVN)), via the nucleus tractus solitarius (NTS). Parvocellular oxytocin neurons are activated including fibers that project to the dorsal vagal motor nucleus (DMX). In this way the endocrine system of the GI tract is activated. Note that the effect of touching is bilateral.

evolutionary, ethological, and medical/oxytocin perspective. We spent numerous weekends at a small charming Austrian pension close to the Konrad Lorenz Institute, writing "Attachment to pets, an integrative view of human-animal relationships with implications for therapeutic practice." Together, we also studied the stress-reducing effects exerted by dogs on young boys exposed to a stress test [258]. During the rewarding discussions in the beautiful surroundings, we also wrote a review article on the oxytocin mediated healing effects of pets, which has been widely read [252]. I also learned a lot about wolves since Kurt Kotrschaal was an expert on this topic, and he and his dog had been living with wolf pups to investigate how their relationship with humans developed over time. The whole group was eventually invited to the Swedish Parliament to present the data on health promoting effects of pets to the minister of Agriculture and some other members of Parliament. This collaboration has been extremely rewarding and productive and the collaboration with Professors Andrea Beetz and Henri Julius is still ongoing. The studies on human-animal interaction have recently been extended to include various aspects of presumably oxytocin-related interactions with dogs, cows and even nature [259,260].

I retired from my professorship at SLU, at the age of 67 around 2010. This really didn't make a big difference; I continued to be associated with my institution at SLU, to travel and give lectures, write articles, and write books like before retirement, the only difference being that I didn't receive a salary.

15.2. Traveling and lecturing

I have always enjoyed lecturing and have been invited all over the world to give lectures about gastrointestinal hormones, oxytocin, breastfeeding, birth, skin-to-skin contact and women's health etc. This activity increased dramatically after I was invited to give lectures on the role of oxytocin in connection with birth at two giant congresses in the Canary Islands and Hawaii, organized by Dr. Michel Odent (2010). Michel Odent has inspired so many women about their rights to give birth and breastfeed in the way they feel is best for them. I am deeply indebted to Michel Odent, who opened up so many avenues for me to learn about female reproduction and allowed me to link it to the concept of oxytocin.

I have learned to deeply admire and respect the people, most often women, involved in the care of women in connection with pregnancy, birth, and breastfeeding, irrespective of country and culture of origin. I have obtained so much information and knowledge from them, and I hope that I have been able to give something back. I have also tried to support those, again most often women, who work with different types of tactile or manual therapies, which may have such positive physical and mental effects on humans at all stages of life. These people often work "in the shadow" as they rarely hold prominent positions in the society and are not well paid, if at all.

15.3. Cost actions (2014 and onwards)

At a meeting in Durban, I met Professor Soo Downe, a very famous research midwife working to promote physiological birth. We started to discuss the possible role of oxytocin during birth outside the classical effect on uterine contractions. Soo Downe was applying for a grant for a COST action regarding physiological birth. The definition of a COST action is as follows: "The European Union EU organizes and finances a specific type of research collaboration within the EU, the COST actions. A COST action is an interdisciplinary research network that brings researchers together to investigate a topic of their choice for 4 years. The European Union funds the cost actions and allows the participants of different levels of seniority to collaborate with representatives from other European countries and to visit each other's countries". Soo Downe included the role of oxytocin in her application to the EU. She received the grant, and I participated in the action. After that, I participated in another COST action, chaired by the midwife Professor Joan Lalor, which was linked to trauma in connection with birth, and now a third one is ongoing. Participating in these COST actions has been very inspiring, and it has generated a lot of knowledge. During these meetings, I have become dear friends with many competent European women, Jane Calleja Agius (Malta), Mechthild Gross (Germany), Sandra Morano (Italy), Ibone Olza (Spain), Claudia Meier Magistretti (Switzerland) and Sarah Buckley (Australia).

15.3.1. Review articles on the role of oxytocin in connection with female reproduction

The oxytocin system plays a very important role in female reproduction, not only by stimulation of milk ejection and uterine contractions during labor. Oxytocin also adapts maternal behavior and physiology to the specific needs during these reproductive periods.

These adaptive effects are induced in response to activation of parvocellular oxytocin neurons from the PVN and of axon collaterals extending from the magnocellular neurons projecting to the posterior the posterior pituitary. Oxytocin is released from the parvocellular neurons and the axon collaterals in response to suckling during breastfeeding or in response to activation of the Fergusson reflex in connection with labor. The Fergusson reflex is activated during labor in response to uterine contractions. The pressure exerted by the baby's head on the lower uterus and cervix activates parasympathetic, sensory nerves which gives rise to oxytocin release from the SON and PVN including the parvocellular neurons from the PVN. (Fig. 16).

To spread existing information on the adaptive physiological and behavioral changes that are induced by oxytocin in the brain during the different phases of female reproduction, I initiated writing review articles together with some other Cost members. We searched databases and summarized all existing data on oxytocin release/levels during pregnancy, birth, skin-to-skin contact postpartum, and breastfeeding [261–265].

15.3.2. Studies at the KI regarding the effects of medical interventions

I continued collaborating with the group of midwives at the KI.

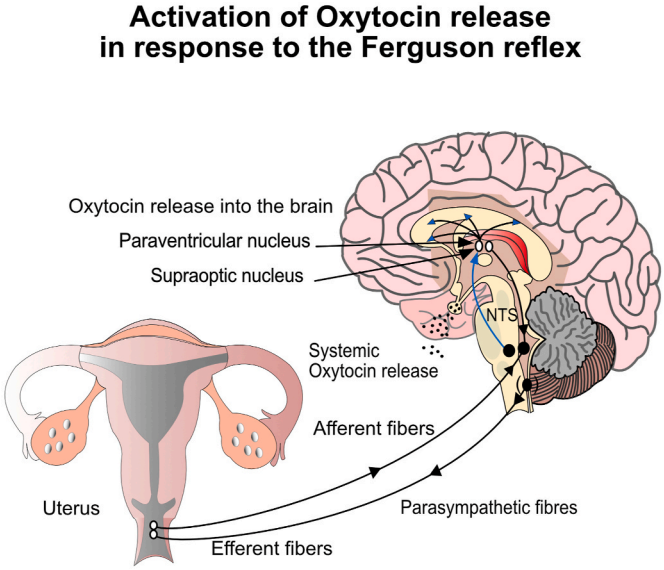

Fig. 16. A schematic illustration of the parasympathetic connection between the uterus and the brain.
Afferent parasympathetic fibers project to the NTS and from there to the oxytocin producing neurons. Oxytocin is released into the circulation from the magnocellular neurons in the supraoptic and paraventricular (SON and PVN) nuclei. In addition, oxytocin is released into different brain structures from the parvocellular neurons of the paraventricular nucleus (PVN). One oxytocinergic pathway projects from the PVN to the parasympathetic ganglia in the lumbosacral region and is part of the efferent parasympathetic pathway.

Medical interventions such as cesarean section, epidural analgesia, and oxytocin infusions may be helpful, even lifesaving, in connection with labor. It has, however, not been sufficiently recognized that medical interventions in connection with birth can disturb the development of the adaptive physiological and psychological effects induced by oxytocin in mother and baby in connection with labor.

15.3.3. Cesarean section

After cesarean section less oxytocin is released in both mother and newborn in comparison to after vaginal delivery, simply because there is no activation of the Ferguson reflex. As a consequence, fewer peaks of oxytocin are released in response to breastfeeding two days after birth. Further, no prolactin is released, and the maternal psychological adaptations are not developed [266,267].

15.3.4. Epidural analgesia and oxytocin infusions

Epidural analgesia is associated with lower levels of oxytocin in connection with birth. In animal experiments both the maternal caring interaction with the newborn and bonding to it, are antagonized by epidural analgesia during labor. In humans, epidural analgesia was associated with lower blood pressure and cortisol levels in connection with breastfeeding two days after birth. In addition, there was no prolactin release or maternal mental adaptations. Epidural analgesia also inhibited the newborns' rooting reflex in connection with feeding two days after birth. In addition, the increase in skin temperature normally seen in babies during breastfeeding was absent. These subtle changes may reflect a partial disturbance of the mother-infant interaction if the mothers had received an epidural in connection with birth two days earlier. The reason for this might be a partial blockade of the afferent Ferguson reflex caused by the epidural. In the absence of the Ferguson reflex, the release of oxytocin from the magnocellular neurons into the circulation as well as from the parvocellular neurons into the brain, will be reduced and consequently the effects of oxytocin will be diminished.

Administration of synthetic oxytocin infusions in connection with birth did not induce an inhibition of maternal adaptations, on the contrary, the release of prolactin was reinforced, and the maternal mental adaptations were clearly expressed. Oxytocin infusions even counteracted some of the endocrine changes induced by epidural analgesia alone. Oxytocin infusions in too high doses may induce stress reactions in mother and fetus, because of its potential to induce too many and too strong uterine contractions leading to a compromised uterine and placental blood flow. In this way mothers will experience increased pain and stress. Exogenous or synthetic oxytocin administered within the recommended dose range does not penetrate the placenta to reach the fetus, but in connection with strong contractions uterine and placental blood flow to the fetus may be compromised, with negative consequences for oxygenation and transport of nutrients. Unexpectedly suckling-related oxytocin levels were significantly lower in mothers who had received both oxytocin and epidural immediately in connection with birth, whereas oxytocin administration or epidural analgesia alone had no effect on oxytocin levels [268–279].

15.3.5. Review articles on the effect by medical interventions on oxytocin in connection with female reproduction

I noted that a lot of misconceptions regarding the role of medical interventions in connection with birth, regarding infusions of synthetic oxytocin, were circulating. Not everybody seemed to understand that endogenous and synthetic oxytocin share the same molecular structure and that the oxytocin from infusions, within the recommended dose range, given to the mother to initiate or augment labor, does not pass the placental barrier in any significant amount, and therefore can't influence the fetus directly. Any effects on the fetus should be mediated indirectly via, e.g., a changed contraction pattern of the uterus. Together with Dr Sarah Buckley (Australia), (my doctoral student) and the midwife Anna Dencker from Gothenburg, all existing data on oxytocin levels/effects after administration of synthetic oxytocin has been summarized [280]. Similar articles regarding oxytocin levels in connection with cesarean section and epidural analgesia are presently being written. Hopefully we will in the future be able to put all this information on the role of oxytocin during labor into a book.

15.4. Closing the circle

15.4.1. The two ways of giving birth

During this period of my research journey, I learned that there are two partly contrasting views regarding how birth should be performed. One group wants women to give birth via vaginal delivery, in a natural way without any medical interventions, in a calm and familiar environment, and surrounded by a supportive person (midwife or doula). The other group sees birth from a more mechanistic perspective and thinks that it is safer to use medical interventions such as cesarean section, epidural analgesia, and synthetic oxytocin infusions to control and speed up the process of birth [281].

Data shows that the duration of birth can, under certain conditions, be shortened by around 2 h by infusions of synthetic oxytocin [281]. There is, however, also data, including meta-analyses, showing that the presence of a supportive person in connection with labor may shorten the duration of birth to a similar degree, i.e., by 2 h. In addition, natural birth makes the experience of birth more positive [282]. Infused synthetic oxytocin, of course, increases activation of the oxytocin receptors in the uterine muscles, which may give rise to more frequent and stronger contractions. On the other hand, there is no mechanistic/functional explanation of how social support can shorten the duration of labor.

When writing a review article on the physiological and pharmacological role of oxytocin during labor for a major obstetrics journal [281], I became aware of the intensity of conflict between people advocating medically controlled and natural physiological births. I tried to include and describe the two alternative ways of giving birth, but some of the reviewers did not appreciate this, which resulted in an overload of questions.

15.4.2. Role of the autonomic nervous system

When writing the review article, I recognized some "anatomical" similarities between the uterus and the stomach/upper GI tract. The uterus, in fact, looks like a stomach turned upside down, and both the uterus and the stomach are provided with afferent as well as efferent parasympathetic and sympathetic nerves.

As described in the beginning of this article, vagal cholinergic activity facilitates gastrin induced HCL secretion and gastric motor activity by increasing the sensitivity/function of the gastrin receptor [20,23]. So, what about the uterus? Could the parasympathetic nervous system sensitize the activity of the oxytocin receptors and thereby increase uterine contractility? Basic physiological mechanisms of this type tend to be of general nature i.e., if they exist in one organ, they are likely to exist also in other organs. There is no recent literature regarding effects of parasympathetic/cholinergic nervous activity on oxytocin induced uterine contractions. However, when I was looking for references for the above-mentioned review article [281], I found experimental data from the 1970s!, showing that autonomic nervous tone facilitates the effect of oxytocin on uterine contractions! Stimulation of the hypogastric and pelvic nerves can by itself stimulate uterine contractions. In addition, the retrieved old articles showed that synthetic oxytocin infusions given in doses that did not induce uterine contractions by themselves did induce uterine contractions during a simultaneous, subliminal electrical stimulation of the pelvic/hypogastric nerves [283,284]. The characteristics of the electrical stimulation used in these studies were the same as those used to induce a vagally induced release of gastrin and insulin and of HCL secretion 14) (Fig. 16).

15.4.3. The doula effect explained?

As mentioned above, several meta-analyses show that the presence of

a supportive companion (a doula) during birth may stimulate the progress of labor and even shorten the duration of labor by 2 h. In addition, the need for medical interventions such as cesarean section, epidural analgesia, and oxytocin infusions is reduced [282]. What is the mechanism behind these positive effects? Touch, closeness, or support does not give rise to a pulsatile release of oxytocin into the circulation. It does, however, increase the activity in parvocellular oxytocin neurons in the PVN, which in turn will stimulate vagal/parasympathetic nervous tone, e.g., to the uterus. This may lead to an enhanced sensitivity/-function of the uterine oxytocin receptors, strengthening the effect of circulating oxytocin on uterine contractility. In this way, touch and support might stimulate the progress of labor and delivery, without increasing plasma oxytocin levels, but instead by increasing the function of the oxytocin receptors. The positive effect on the progress of labor by the presence of supporting persons and familiar surroundings may correspond to the "cephalic phase" of a vagally-mediated activation of gastrointestinal function.

Why have these findings regarding the role of the autonomic nervous system on uterine contractions been forgotten? Probably because research is trendy. Certain research subjects and techniques are popular during specific periods of time and are then substituted by others. If you apply for money for research, you must include research questions/mechanisms that are "en vogue"; if you don't, you will not receive any research grants. Probably the research front moved on and left some basic research questions, such as the functional cooperation of hormones and autonomic nervous tone in the uterus, behind. Another reason for not finding these old studies is, of course, the fact that researchers of today don't always read old articles. Why?

16. Writing books

I have always loved lecturing, particularly when speaking freely and not reading a text. Around 2000, I started to develop a new type of writing skill, i.e., writing about scientific data for people who are not scientists. It took a while to find the free flow of words, since the scientific, structured, language, which was difficult to get rid of. Until now, I have written five books on oxytocin by myself and three in collaboration with other authors. The first book on oxytocin, *The Oxytocin Factor, the Hormone of Healing and Closeness* (2002), is available in 11 different languages, and the second one, *Oxytocin, the Hormone of Closeness (2009),* in 5 languages. *Oxytocin, the biological guide to motherhood,* includes many references, both preclinical and clinical. It was originally published in the US by Thomas Hale and was later on transferred to Preclaeerus press (Kathleen Kendall Tackett). *Why Oxytocin Matters* (2020) describes the role of oxytocin in normal physiological birth and is published by Pinter and Martin in England.

Attachment to Pets (2012), written together with Henri Julius, Andrea Beetz, Kurt Kotrschal, and Dennis Turner, was originally published in German. It includes evolutionary, ethological, physiological, and psychological aspects of the human-animal bond and has been translated into four languages.

The two last books, *Hundstund,* Natur & Kultur 2022 and *Medfödd, förmågan att vara förälder*, Carlssons förlag 2024, are in Swedish and describe the role of oxytocin in the interaction between dogs and humans and in parenthood, respectively for laymen.

17. Clinical treatment with oxytocin

17.1. Oxytocin and its role in the regeneration of tissues and cells

As discussed in detail above, oxytocin stimulates the function of the endocrine system of the GI tract, and thereby, it promotes processes linked to growth and healing. Oxytocin also facilitates wound healing and local restorative processes by increasing circulation and the uptake of oxygen and nutrients locally in tissues. The potent anti-inflammatory and stress-reducing effects also contribute to the restorative effects of oxytocin [240,241]. In addition, oxytocin may increase the reproduction of individual cells, including certain types of stem cells [285], and it has been shown to restore the degeneration of muscle tissue [286].

17.1.1. Oxytocin regenerates atrophic vaginal mucosa; clinical studies

I assumed that, as oxytocin promotes wound healing, oxytocin might also promote cell generation in connection with atrophic conditions, e.g., vaginal atrophy. In collaboration with Professors Ulf Ulmsten and Christer Sjögren at the Department of Obstetrics and Gynecology at the Akademiska Sjukhuset in Uppsala, in vitro experiments were performed, which showed that oxytocin dose dependently induced regeneration of vaginal epithelial cells obtained from menopausal vaginal biopsy material and in addition, but less potently from vaginal epithelial cell lines ([287]. Based on these results, a small double-blind, placebo-controlled clinical study, in which the effect of local intravaginal application of an oxytocin-containing gel on vaginal atrophy was investigated, together with professors Britt Marie Landgren and Aino Fiano-Jonasson at Huddinge Hospital (part of KI) around 2000. One week of local vaginal treatment with an oxytocin-containing gel sufficed to restore the number of cell layers (from 2 to 4 to 12–14) in the vaginal mucosa. Data was obtained based on histological examination of vaginal biopsies collected before and after treatment. Also, visual inspection revealed that the vaginal mucosa looked healthier, and the women expressed that they felt better [288].

Two more successful, double blind, placebo-controlled clinical studies and one pharmacokinetic study were performed. The results, based on cytological investigation of vaginal smears, showed that local intravaginal administration of oxytocin gave rise to a more mature pattern of vaginal cells, which supported the previous finding of a rejuvenating effect of oxytocin on atrophic vaginal mucosa [289–291]. In 2017, the results of a third study unexpectedly did not show any positive effect of oxytocin. I suggested that an investigation should be performed to identify the reason for the study's negative results. The company, however, decided to end the oxytocin project after this unsuccessful study.

In 2020 an Egyptian study was published in a peer-reviewed journal that showed the positive effects of the local intravaginal application of oxytocin on vaginal atrophy. The results were identical to those initially shown by my collaborators in 2000 [288,292], and soon thereafter, a similar positive study was published by an Iranian research group [293].

An additional double-blind, placebo-controlled clinical study regarding the effect of intravaginal administration was performed in Egypt. This study showed positive results, which have been published [294]. Additional studies are planned.

18. Summary

I am so grateful to Professor Sue Carter, who has allowed me to write this review article. It has been inspiring to take this journey back in time and to remember the different phases of my scientific career. I was surprised to re-experience the enormous enthusiasm and joy that I experienced during my first 30 years in research, when I studied and tried to describe the enormous "intelligence" and the growth-promoting, reproductive and restorative or healing effects of the oxytocin system and of the endocrine system of the GI tract. Negative experiences of course also reappeared while summarizing certain parts of my scientific research story. Fortunately, my passion for research, giving talks and writing is still intact in spite of some difficult interludes.

It is fascinating to see, in retrospect, how the different research projects follow each other in an organic way, even if these connections were not always clear to me at the time. It is if the oxytocin system is part of the unconscious. My view on the role of oxytocin has also changed over time. Originally, I thought that oxytocin was a system connected to "calm and connection," and yes, it is, but not always. Under certain conditions, oxytocin may act in the opposite direction and induce stress-like effects, such as elevation of blood pressure and retardation of

growth. These contrasting findings regarding the effects of oxytocin make sense only if oxytocin is regarded as a life-promoting system. From this perspective, it is to be expected that oxytocin induces a rise in blood pressure in unfamiliar surroundings and that oxytocin-linked promotion of growth is restricted when there is too little to eat. The inner and outer environments are of great importance for the expression of the oxytocin effect pattern. This is, of course, of great importance for survival.

When looking back at the difficult periods of my scientific life, it is obvious that I am not the only person who has experienced resistance during my career. It is obvious that I didn't see or experience any problems being a woman during my first ten years in science when I worked with gastrointestinal hormones. The problems came when I left the well-defined and established research and started to work with a new research line chosen by myself i.e. physiology related to female reproduction and oxytocin. This is probably to a certain extent a general phenomenon. Still, I think that some of the anger and wish to exclude that my research or perhaps my person evoked in the scientific community has something to do with gender issues. It may be easier to support and work with those similar to yourself, and it is easier to accept research subjects that follow the contemporary and one's own lines of thought. In this way, science is conservative. The paradox is that even if I was excluded, my research obviously evoked interest since it was, in part, taken over by others.

Of course, this is all history now, but hopefully, these reflections might give other women in science some food for thought.

CRediT authorship contribution statement

Kerstin Uvnäs Moberg: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

Kerstin Uvnäs Moberg, MD, PhD and professor emerita in Physiology does not receive any funding. She holds stock in the Company Oxagon, which is performing clinical studies in which locally applied oxytocin is used to treat vaginal atrophy in menopausal women.

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