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Oxytocin may have a therapeutical potential against cardiovascular disease. Possible pharmaceutical and behavioral approaches

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A B S T R A C T

Based on the ancient role of oxytocin and its homologues as amplifiers of reproduction we argue for an evolutionary coupling of oxytocin to signaling pathway which support restorative mechanisms of cells and tissue. In particular, the survival and function of different categories of stem cells and primordial cells are enhanced by mitogen-activated protein kinase (MAPK) pathways. Furthermore, oxytocin stimulates the AMP-activated protein kinase pathway (AMPK) in numerous of cell types which promotes the maintenance of different cell structures. This involves autophagic processes and, in particular, may support the renewal of mitochondria. Mitochondrial fitness may protect against oxidative and inflammatory stress - a well-documented effect of oxytocin. The combined specific trophic and protective effects oxytocin may delay several degenerative phenomena including sarcopenia, type-2 diabetes and atherosclerosis. These effects may be exerted both on a central level supporting the function and integrity of the hypothalamus and peripherally acting directly on blood vessels, pancreas, heart, skeletal muscles and adipose tissue etc. Furthermore, in the capacity of being both a hormone and neuromodulator, oxytocin interacts with numerous of regulatory mechanisms particularly the autonomic nervous system and HPA-axis which may reduce blood pressure and affect the immune function. The potential of the oxytocin system as a behavioral and molecular target for the prevention and treatment of cardiovascular disease is discussed. Focus is put on the affiliative and sexual significance and the different options and limitations associated with a pharmaceutical approach.

MeSH: Aging, Atherosclerosis, Heart, Hypothalamus, Inflammation, Love, Orgasm, Oxytocin.

Background

Members of the oxytocin/vasopressin family have presumably been around for about 600 million years since homologues of these non-apeptides can be found in primitive invertebrates as nematodes and annelids [1]. Similar to what is the case in humans and other mammals, the peptides are important in primitive organisms for behavior and muscle contractions involved in reproduction.

The nematode Caenorhabditis Elegans has extensively been applied to study the connection between reproduction and life span. In this worm primordial egg cells may produce a compound which compromises the autophagy function. Autophagy is important for cell maintenance as it eliminates dysfunctional components such as misfolded proteins and defective mitochondria. The removal of the germ line cells therefore expands the lifetime of the animal [2]. The mechanism that impairs autophagy appears to be intertwined with the mobilization of fat as energy for the offspring [2]. Such a link between reproduction and degeneration, possibly leading to death of the progenitor, may be profitable for primitive organisms with a fast reproduction when the resources are confined. However, in species which have developed a strategy to reproduce more than once or where the offspring requires nursing, measures are needed to counteract the degeneration and death of the parent. An evolutionary coupling between reproductive signaling and the protection against decay of the mother therefore appears to be likely. In general, this would also favor sexually active individuals rather than individuals not contributing to the progress of the population. In this context, it would be plausible to suggest an early development of associations between oxytocin homologues and cell protective pathways that may have been preserved in humans.

Hypothesis

Oxytocin has some general antioxidative, anti-inflammatory and restorative properties which gives this peptide a potential as a remedy for the protection and treatment of cardiovascular disease. Based on biological research and epidemiological findings we discuss how to approach the oxytocin system by pharmaceutical and behavioral avenues.

Oxytocin may protect against oxidative stress and inflammation by interfering with intracellular energy managing systems

Oxytocin may exert some of its protective effect by the stimulation of the AMP activated protein kinase (AMPK) pathways. AMPK is

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suggested to be an ancient general sensor of a low energy status of the cells, as it is activated as a result of low levels of the ATP/AMP ratio. Its activation normally causes the cell to switch from an anabolic to a catabolic state by the stimulation of glycolysis and fat oxidation and inhibition of triglyceride, glycogen, protein syntheses and other ATP requiring processes. This prevents that an energy deficit builds up in the cell [3]. In addition to being activated by a declining energy level, AMPK activity is also enhanced with increasing level of Ca^{2+} by the Ca^{2+}/calmodulin-dependent protein kinase (CAMK) pathway. This may be an important mechanism during muscle contractions [4]. The contractive effect of oxytocin on smooth muscles is elicited via its G-protein coupled receptor mediating an increased intracellular concentration of Ca^{2+} [5]. However, in skeletal muscles oxytocin has been demonstrated to have the potential to enhance the Ca^{2+} concentration to a subcontractive level which induces an activation of AMPK [6]. Without yet being confirmed, oxytocin might also activate AMPK in non-contractive cell types.

A capacity of oxytocin, in this way, to promote a general fuel mobilization at the expense of energy storage in the mother may have evolved to facilitate the provision of nutrients for the offspring. In addition to the mild catabolic effect, the activation of AMPK may improve the efficiency and capacity of respiration by supporting the fitness of the mitochondria. In this context, AMPK has been demonstrated both to promote the autophagy of damaged mitochondria and to support the construction of new [7]. Replacement of defective mitochondria may also be important to minimize mitochondrial production of Reactive Oxygen Species (ROS) as demonstrated in yeast [8]. It is well established that ROS damage different cell components including DNA, lipid membranes, proteins and, in particular, the mitochondria and may accelerate the development of degenerative diseases [9,10]. Apart from its stimulation of mitochondria renewal, increased AMPK activity may also lead to the upregulation of UCP2, an uncoupling protein with an acute regulatory impact on the ROS production of the mitochondria [11]. Elevated ROS levels are linked to an increased inflammatory activity where stimulation of the NF-κB pathway may be an important factor [12]. In this context, the anti-inflammatory effects of several different hormones and drugs has been proposed to be mediated by AMPK indirectly acting on NF-κB [13]. ROS produced by the mitochondria appears to be important for the immune response as demonstrated in UCP2 knock-out mice which were more resistant against infections but more liable to develop atherosclerosis and autoimmune diseases [14].

In addition to the UCP's, an uncoupling function of the mitochondrial ATP-dependent potassium (mitoKATP) channel has been suggested to play a crucial protective role against reperfusion damages when oxytocin was administered in an *in-situ* study with rat hearts [15]. A later study from the same group supported an important role of Nitric Oxide (NO) in this cardioprotective effect of oxytocin [16]. This is plausible, as the vasodilatory effect of oxytocin may depend on a NO release from the endothelium [17].

Mammalian target of rapamycin (mTOR) is another part of the energy responsive system of the cells. In its active form this serine/threonine protein kinase stimulates growth including protein and lipid synthesis whereas it generally inhibits autophagy [18]. mTOR is activated by growth factors conditioned by some amino acids [18] but is inhibited by AMPK [19]. A high AMPK activity induced by oxytocin may in this way increase the level of autophagy. However, the function of oxytocin as a mild catabolic hormone is emphasized by its potential to inhibit mTOR independently of AMPK [20].

Several studies applying different models both in mammals and invertebrates have reported that life and health span can be extended substantially by inhibition of the mTOR pathway. An improved mitochondrial function with a reduced formation of ROS may be an important factor in the life extending effect of the TOR-inhibitor rapamycin [21]. In mice where the mTOR gene has been manipulated only to be expressed at a level of 25% lived on average 22% longer without any changes in their metabolic profile compared to the wild type mice. Furthermore, the manipulated mice demonstrated less aggregation of defective proteins with age which may be interpreted as an improved autophagy [22]. Some of the beneficial effects of exercise [23] and caloric restriction [24] has been proposed to involve the same catabolic pathways.

Thus, the mechanisms of oxytocin to ensure sufficient nutrient supply by promoting catabolic mechanisms and respiratory efficiency may at the same time dampen oxidative stress and stimulate the maintenance systems of the cell. This could be considered to have evolved as a fortunate byproduct of oxytocin's engagement in muscle contractions and the associated Ca^{2+} mediated pathways. Hence, the role of Ca^{2+} as a second messenger beyond what is required for contraction can also be applied by oxytocin in noncontractile cells.

Oxytocin promotes cell maintenance systems and restorative processes by Ca^{2+}-independent pathways

Oxytocin stimulates, by its G-protein coupled receptor, several signal transduction systems which probably never have been responsible for muscle contractions. In this context it is important to mention the Akt and ERK1/2 pathways which promote survival of stressed cells. ERK signaling is a mediator of oxytocin's stimulation of prostaglandin-2 (PGE-2) production [25]. Increased PGE-2 release is well established as an important mechanism for oxytocin to initiate myometrial contractions during labor [26]. However, PGE-2 also appears to have a pivotal role by promoting the survival and proliferative capacity of different types of stem cells [27]. By supporting stem cell function oxytocin may have acquired a general capacity to preserve the integrity of different tissues. This exemplifies that the oxytocin/vasopressin family also has evolved a function as a general strength-enhancing and life span extending factor.

In particular, the capacity of mesenchymal stem cells (MSC) and different progenitor cells to repair various tissue damages appears to be enhances by oxytocin. Focus has been put on the treatment of myocardial infarctive lesions with MSC. Thus, the proliferation and chemotaxis of rat bone marrow MSC was increased when incubated with oxytocin at a concentration of 10^{-10} M [28] corresponding to about high physiological blood concentrations. In the same study, MSC also demonstrated a greater survival rate during starvation and hypoxia when treated with oxytocin. However, these effects of oxytocin were ablated when the cells contemporarily were treated with substances which blocked the Akt and ERK1/2 pathways. Furthermore, a protective effect against apoptosis of isolated cardiomyocytes during exposure to hypoxia and starvation was observed when the cells were cocultured with MSC. This impact on MSC on the cardiomyocytes was reinforced when the MSC have been conditioned by oxytocin. This indicates the presence of guarding paracrine effects from stem cells which can be enhanced by oxytocin. Accordingly, the secretion from MSC of a number of cytokines related to growth, migration and survival was found to be increased when the cells were treated with oxytocin.

A stimulation of the ERK1/2 pathway also seems crucial when oxytocin exerts an antisenescent effect on dermal fibroblasts. When cultured in a medium conditioned by senescent fibroblasts, non-senescent fibroblasts achieved from young women were found to acquire the senescence-associated secretory phenotype (SASP) characterized by an increased production of proinflammatory cytokines [29]. This illustrates a capacity of senescent cells to inflict senescence on neighboring cells by paracrine effects causing them to go into cells cycle arrest which may compromise tissue repairment. However, when oxytocin was added to the conditioned media senescence of the fibroblasts was delayed and the proliferative capacity of the cells was protected. Moreover, the beneficial effect of oxytocin was abolished if ERK1/2 signaling was blocked by a MAPK kinase inhibitor.

ERK1/2 signaling also seems to be important for the role of oxytocin in its ability to support the repair and maintenance of skeletal muscles.

Studies on mice have indicated that a declining oxytocin function with age may contribute to sarcopenia and the decreased capacity for muscles to repair in old individuals [30]. Muscles in old mice are characterized by a blunted tendency of satellite cells to differentiate into muscle cells, but this decline can be counteracted by oxytocin. Accordingly, oxytocin treatment of old mice was found to restore muscles repairment after an injury to a level similar to that of the young mice. In contrast, muscle repairment in the young mice was impaired by blocking the effect of oxytocin. Furthermore, in the same article, leg muscle atrophy was observed to be more pronounced in old oxytocin knockout mice compared to wild-type mice. The involvement of the ERK1/2 pathway in the activation by oxytocin of satellite cells was supported by the observation that the proliferative effect of oxytocin on satellite cells collected from damaged muscles tissue was abolished when an inhibitor of this pathway was applied.

Oxytocin may play a very important role in the renewal and protection of various types of mucosal linings and dermal tissue. A study in rats has demonstrated that intraperitoneally administered oxytocin ameliorated injuries on ileal mucosa induced chemically or by radiation [31]. The protective effect of oxytocin was eliminated by co-administration with a PGE-2 inhibitor. In the same article, oxytocin was reported to trigger pulsatile PGE-2 release in small intestine dissected from rats. Furthermore, a proliferative impact of oxytocin on the gut mucosa is supported by findings of shortened villi and crypts in oxytocin receptor knockout mice accompanied by an increased susceptibility to colitis inducing agents [32]. In humans, topical treatment with oxytocin gels has been found to ameliorate postmenopausal atrophy of the vaginal mucosa [33–35] which may be explained by an improved maturation and proliferation of the epithelial cells [36]. An accelerated healing of inflicted skin wounds obtained by probiotic treatment with *Lactobacillus Reuteri* has been reported from mouse and human experiments [37]. *L Reuteri* supplementation to the drinking water was found to upregulate oxytocin activity in mice and the healing promoting effect of the bacteria was abolished in an oxytocin knock-out model [38]. Oxytocin has also been suggested to be involved in a faster wound healing process found associated with a positive marital behavior [39]. Oxytocin mediated mechanisms in the brain which supports peripheral tissue survival may exist as indicated by an experiment where the survival of surgically constructed dorsal musculocutaneous flaps was improved in rats by intracerebroventricularly injections of oxytocin [40]. The authors proposed that IGF1 and other growth factors could be involved.

Oxytocin may also protect pancreatic islets cells during metabolic and inflammatory stress which may be important to delay the development of type-2 diabetes. In this regard, the ERK1/2 signaling pathway also appears to be pivotal. This was indicated by a study on oxytocin receptor knockout mice ($OTR^{-/-}$) being fed a high fat diet [41]. The pancreas of the $OTR^{-/-}$ mice did not demonstrate a pathological phenotype after a normal dietary regimen and their glucose tolerance was similar to what was observed in the wild-type mice. However, glucose tolerance was more impaired in the $OTR^{-/-}$ mice after a high fat diet accompanied by a reduced insulin response compared to the wild type mice. Furthermore, islets samples showed a greater number of dead and apoptotic cells in the $OTR^{-/-}$ mice than in the wild-type mice after the high fat diet. The further finding that active phosphorylated form of ERK1/2 was less abundant in the islets cells of the $OTR^{-/-}$ mice compared to the wild-type mice after a high fat diet suggests that ERK1/2 signaling is involved in the protective effect on islets cells of intrinsic oxytocin. Possible protective and maintenance mechanisms mediated by ERK signaling are outlined in Fig. 1.

Oxytocin protects against inflammatory stress and degeneration – evidence from laboratory experiments

A number of animal experiments have documented a significant protective potential of oxytocin both against inflammatory crises and different slowly progressing degenerative processes. This is the case for studies on isolated organs as well as living animals. The effects of oxytocin may be conveyed from the hypothalamus both by humoral routes and by the autonomous nervous system. Furthermore, different other organs are capable to synthesize oxytocin including the heart [42], gut [43], skin (keratinocytes) [44], prostatic glands [45] and gonads [46].

An acute direct cardioprotective effect of oxytocin has been demonstrated in different investigations. In ischemia-reperfusion (IR)-studies on rats hearts a decreased infarct size, a decline in arrhythmic incidences and a better hemodynamic control was found when oxytocin was administered intraperitoneally prior to the ischemia [15,16]. The involvement of NO in a cascade which promotes antioxidative functions may be important for the protective effect of oxytocin as it could be abolished by a nitric oxide synthase inhibitor. An IR study on the kidneys has accordingly demonstrated an ability of oxytocin to protect renal function, to reduce the oxidative stress (less lipid peroxidation) and to attenuate the inflammatory response [47]. Oxytocin has also been reported to mitigate the damages with IR in the liver likewise accompanied by dampened inflammatory reaction [48]. Furthermore, subcutaneous administration of oxytocin resulted in a reduction in the blood level of the inflammatory cytokine TNF-α and markers of oxidative stress in the stomach during extensive thermal skin trauma in rats [49]. The latter study indicates that oxytocin may have a relieving effect on systemic traumatic conditions.

The mechanisms and intra-cellular pathways by which oxytocin may protect the vascular system has been discussed in a recent exhaustive review [50] and the present article will therefore mostly be restricted to focus on particular biological, behavioral and treatment issues. Inflammation accompanied by oxidative stress of the vascular wall is well established in the etiology of atherosclerosis and research to approach the disease by anti-inflammatory drugs is in its infancy [51]. Increased adhesion to the endothelial cells of activated macrophages promotes the transfer of oxidized LDL-particles into the arterial wall. This is suggested as a major inflammatory mechanism to accelerate plaque formation.

Long term antioxidative and anti-inflammatory effects of oxytocin may therefore have a delaying impact on the progress of cardio-vascular diseases. Several studies support an antiatherogenic potential of oxytocin. I heritable hyperlipidemic rabbits, the development of aortic atherosclerotic lesions was reduced when the blood level of oxytocin was constantly elevated via infusion pumps [52]. In this study, the oxytocin infusion had no significant effects on blood lipids and cortisol level. However, C-reactive protein was lower indicating a systemic anti-inflammatory effect of oxytocin. Similar results with oxytocin infusion have been reported from a study on hyperlipidemic $ApoE^{-/-}$ mice, where the antiatherogenic effect of oxytocin was accompanied by decrease in the secretion of the proinflammatory cytokine IL-6 from epididymal fat tissue [53]. However, local anti-inflammatory effects on the arterial wall may add to the systemic effects of oxytocin. Thus, a diminished IL-6 secretion and NADPH oxidase dependent superoxide production was seen in incubated endothelial cells, vascular muscle cells and macrophages when oxytocin was added to the medium in physiological concentration [54]. Oxytocin has also been reported to mitigate the vascular damages caused by general oxidative stress imposed by adding methionine to the chow in rats. The methionine supplementation led to thickening of the aortic wall and elevated levels of NF-κB protein in the vascular tissue, but daily intraperitoneal administration of oxytocin was found to counteract these effects [55].

Dysfunctional mitochondria may be crucial in the pathogenesis of atherosclerosis. Most of the mitochondrial proteins are encoded for in the nucleus but some of the genes which code for proteins that constitutes the respiratory complexes are still situated in the mitochondria where they are more vulnerable to mutations. It is hypothesized that such mutations accumulate with increasing age of the organism resulting in the impairment of the electron transfer through the

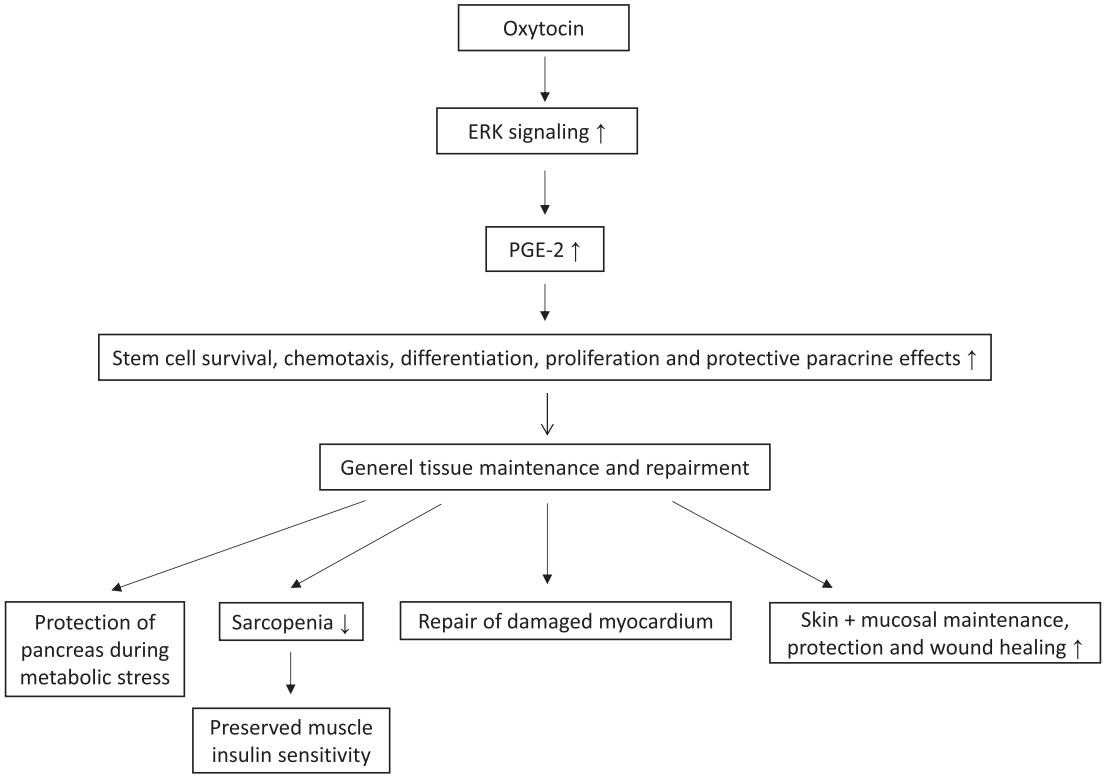

Fig. 1. General effects of oxytocin mediated by ERK signaling.

complexes. This would cause an increased ROS production due to superoxide formation by oxygen being reduced by escaped electrons [56]. The ROS formed could further damage the mitochondrial DNA leading to the constitution of a vicious cycle. If the defective mitochondria are not eliminated, they would increase the oxidative burden of the cell which, in turn, also may augment the inflammatory activity. The idea, that dysfunctional mitochondria may play a role in atherosclerotic plaque formation is supported by findings of abnormal mitochondrial morphology and greater variation in mitochondrial genes in samples taken from atherosclerotic plaques compared to samples from the normal intima [57]. The importance of ROS derived from the mitochondria in vascular aging processes is supported by a study with transgenic mice expressing a human catalase gene in their mitochondria [58]. The manipulation resulted in a 50x higher expression of catalase in their heart mitochondria compared to the wildtype. Catalase is an enzyme which reduces the ROS activity by converting hydrogen peroxide to oxygen and water. Less atherosclerosis of the cardiac arteries was seen in the transgenic mice at the age of about 20 months. Furthermore, the transgenic mice lived significantly longer (about 20%) and pathology examinations of their heart showed fewer sign of myopathy.

One study supports that oxytocin may alleviate the consequences of mitochondria being stressed by long-term environmental factors. Mice which have been stressed as pups by separation from their mother during a 3-hour period each day demonstrated depressive-like behavior later in life accompanied by an elevated inflammatory state and oxidative stress in the hippocampus [59]. Furthermore, ROS production was increased in mitochondria isolated from hippocampus. If oxytocin was injected intracerebroventricularly prior to the behavioral tests the stressed mice performed better in the tests and showed less hippocampal inflammation with an improved mitochondrial function.

A direct anti-inflammatory effect of oxytocin has been supported by several experiments both on local and systemic levels. Subcutaneous injection of oxytocin has been reported to ameliorate the injuries caused by intracolonic administration of acetic acid. This was accompanied by a blunted serum response of TNF-α [60]. In another study, the inflammatory response to injection of carrageenan under the skin was attenuated by coadministration of oxytocin [61]. The presence of an anti-inflammatory role of oxytocin in the skin has also been supported by *in-vitro* experiments with human skin cells [62]. In that study, cultured keratinocytes had an increased secretion of pro-inflammatory cytokines if their oxytocin receptor had been knocked down by a small interfering RNA technique. In a study on healthy men, an attenuated systemic inflammatory response (including fever) to a bolus infusion of bacterial endotoxin has been observed with intravenous administration of oxytocin [63]. In an *in-vitro* test, incubation with oxytocin of macrophages which were sampled from rat bone marrow and differentiated caused them to secrete less TNF-α [64]. Accordingly, in the same publication, adipose tissue of dietary obese rat was reported to have a reduced TNF-α expression when the animals had been treated with oxytocin. Adipose tissue secretion of another important proinflammatory cytokine, IL-6, has also been found to be diminished by oxytocin treatment [53]. Possible anti-inflammatory mechanism of oxytocin is outlined in Fig. 2.

Inflammation and adipocyte regulation in the metabolic syndrome

A dampening of the general inflammatory status of the body may be an important preventive measure against cardio-vascular diseases. This may particularly apply to elderly or overweight individuals where the systemic inflammatory activity is more pronounced. Apart from the direct damaging effect on the arterial wall, inflammatory stress may also exert an impact on pancreas, muscles, liver and brain which may be detrimental to the blood vessel by secondary avenues. Pro-inflammatory cytokines produced in the adipose tissue may contribute with an important share to the general inflammatory level. Visceral obesity as a risk factor for atherosclerosis has to a large extend been attributed to the inflammatory activity of the adipose tissue itself [65]. This can be explained both by a direct promoting effect on atherosclerotic lesions and by a detrimental impact on the insulin function.

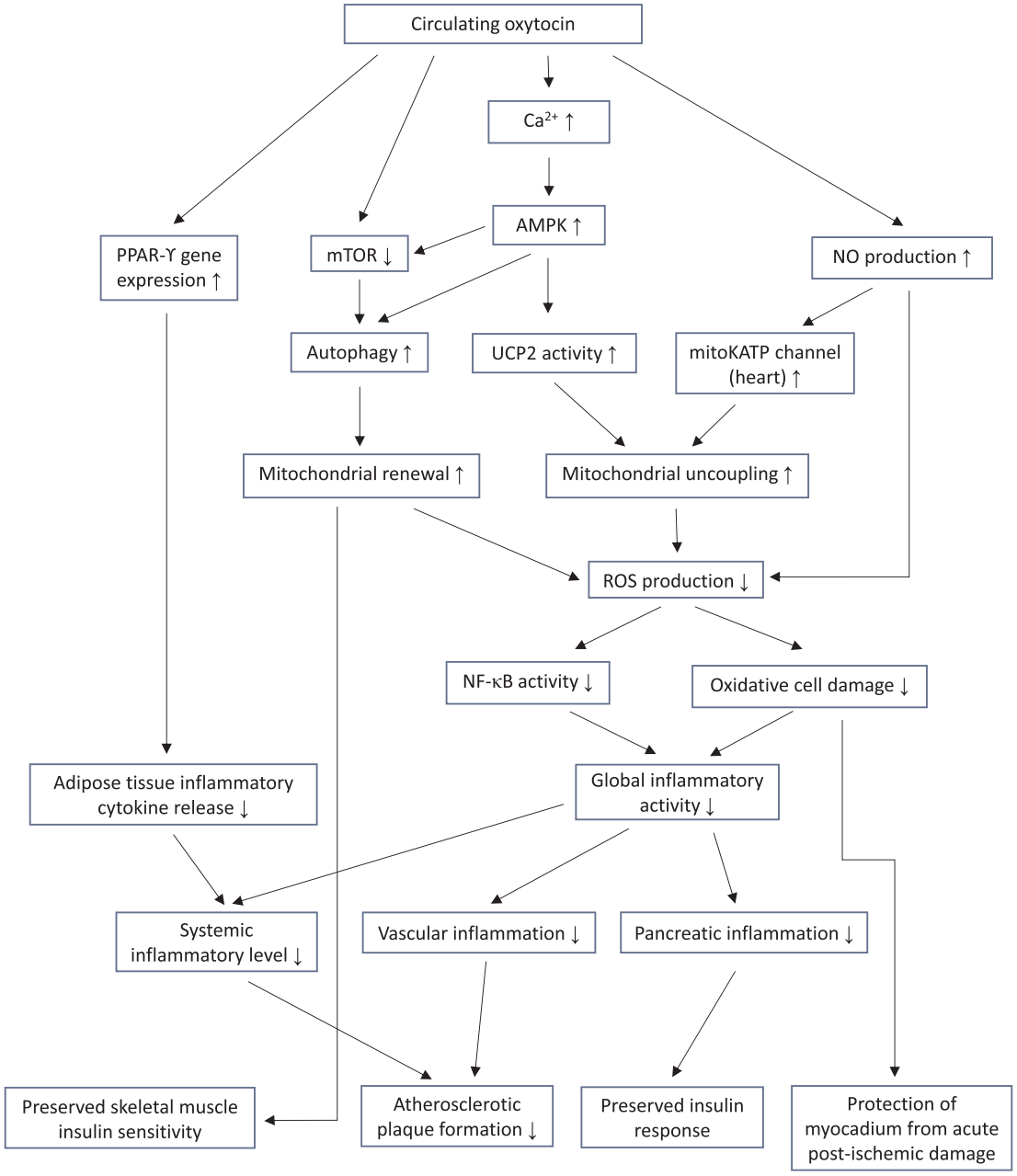

Fig. 2. Anti-inflammatory mechanisms of oxytocin.

However old age, per se, is associated with a reduced insulin sensitivity as demonstrated in a study where young and elderly men with similar body composition were compared [66]. A decreased glucose tolerance in the elderly men was accompanied by a greater fat accumulation in the skeletal muscles and liver. Furthermore, they showed a reduced in vivo oxidation and phosphorylation activity in the skeletal muscles indicating an impaired mitochondrial function. Accordingly, decline in respiratory rate and capacity with age has been demonstrated in muscle homogenates in an early human study [67]. In addition to a compromised capacity for glucose uptake by the skeletal muscles, an eroded mitochondrial function may contribute to the general age-associated enhancement of the inflammatory activity. Moreover, an increased secretion with age of proinflammatory cytokines by adipose tissue may be an important factor to enhance the systemic inflammatory level. Visceral adipose tissue sampled from old rats have been shown to express more TNF-α, IL-6, IL-1β but less PPAR-γ compared to what was found in young rats [68]. PPAR-γ has been found to be an important attenuating factor for the immune response in adipose tissue but also in other organs including the brain [69].

Apart from being a transcription factor which counteracts the production of proinflammatory cytokines, PPAR-γ is a key promoter of adipocyte differentiation and proliferation [70]. A reduced PPAR-γ activity with age may therefore be involved in the attenuated capacity of preadipocytes and adipocytes to differentiate, proliferate and preserve their role as a lipid storing entity [71]. This could be a crucial part of the age-related pathology leading to insulin resistance and cardiovascular disease. An enhanced gene expression of PPAR-γ in visceral adipose tissue has been observed in rats subcutaneously infused with oxytocin during a 2-week period which resulted in plasma concentrations of approximately 6x the basal level [72]. Accordingly, the size of the epididymal adipocytes was reduced by oxytocin indicating a proliferative effect of the peptide. Large visceral adipocytes reflecting a poor proliferative activity have been found to be a strong marker of an atherogenic blood lipid profile, insulin resistance and liver damages in

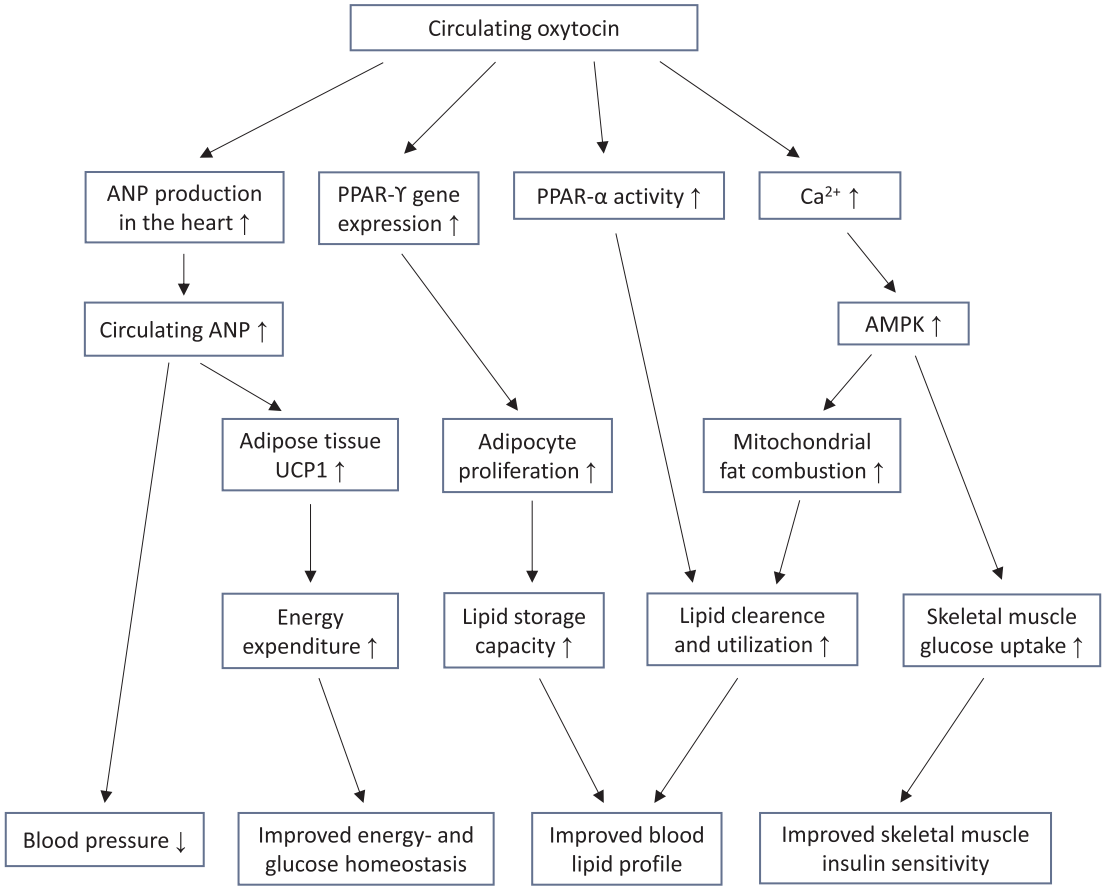

Fig. 3. Effects of circulatory oxytocin on cardiovascular risk profile.

obese humans [73]. Furthermore, the increased PPAR-γ expression in the oxytocin treated rats was accompanied by an elevated expression of adiponectin, which is an adipokine with anti-inflammatory and anti-atherogenic properties [74].

An adipogenic effect of oxytocin appears to be contradictory to its role as a nutrient mobilizing hormone. However, a possible promotion of fat storage by the upregulation of PPAR-γ may be counteracted by a contemporarily promotion of the PPAR-α activity. Thus, intracerebroventricular infusion of oxytocin in rats leading to increased hypothalamic oxytocin gene expression and elevated plasma oxytocin concentrations has been reported to upregulate the synthesis of oleoylethanolamide in epididymal adipose tissue [75]. Oleoylethanolamide is an activating ligand for PPAR-α. PPAR-α is a transcription factor for several enzymes involved in uptake and oxidation of fat including lipoprotein lipase, hormone sensitive lipase, and acyl-CoA oxidase. Accordingly, an augmented gene expression of these enzymes by oxytocin was seen in that study. The central oxytocin infusion also resulted in a lower plasma triglyceride concentration whereas that of glycerol was increased indicating an enhanced blood lipid uptake and adipose tissue lipolytic activity, respectively. In relation to lipoprotein lipase expression it might have been interesting if other organs had been examined including liver, skeletal muscles and heart where the expression of PPAR-α is more prominent [76].

The overall impact of oxytocin on fat metabolism therefore appears to be a promotion of the utilization of fat as a fuel by the enhancement of enzyme activity involved in fat oxidation. Such an effect seems plausible considering that nursing may increase the likelihood for the mother to face a state of negative energy balance. Observations of a reduced respiratory quotient after treatment with oxytocin both in a pair-feeding experiment with rats [75] and acutely in fasting humans [77] support this notion. Furthermore, the concomitant increase in triglyceride clearance and lipolysis in adipose tissue induced by oxytocin has been suggested to accelerate futile cycle thermogenesis [78]. A thermogenic effect of oxytocin has been confirmed in rats by a blunted weight gain during high-fat feeding compared to pair-feed control rats [75]. An important role of oxytocin in thermoregulation has been demonstrated in oxytocin knock-out mice showing an impaired capacity to defend their body temperature during cold exposure [79]. The thermogenic potential of oxytocin may have evolved by the need to protect the pups from hypothermia. However, at the same time, an increased energy expenditure may contribute to the weight loss observed in humans [80] and rhesus monkeys [81] when treated with oxytocin for several weeks.

The improving effect of oxytocin on skeletal muscle insulin sensitivity may involve activation of AMPK

Kinase activation of AMPK in the skeletal muscles has been proposed as an important factor for substrate mobilization during strenuous and endurance exercise. In this context, both contraction- and insulin dependent glucose uptake may involve the activation of AMPK [82]. Oxytocin may support this system during metabolic challenges. An increased glucose uptake has been reported to be induced by oxytocin in C2C12 myoblast [6] and cardiomyocytes from newborn rats [83]. In both cases, this effect was abolished by blocking the AMPK pathway. The effect of oxytocin on glucose uptake was potentiated when metabolic stress was imposed on the cardiomyocytes suggesting a protective capacity of oxytocin e.g. during hypoxia.

In addition, AMPK also plays a role in the mobilization of fat as a fuel. Malonyl-CoA synthesized by acetyl-CoA carboxylase is a gatekeeper of fatty acid entering of mitochondria for oxidation. Activated AMPK enhances fat oxidation by inhibiting acetyl-CoA carboxylase.

Consequently, a compromised AMPK function may lead to a reduced insulin sensitivity of the skeletal muscles [84] with myocytes showing excessive lipid accumulation as a phenotypic marker of a poor fat oxidation capacity and insulin resistance. A deteriorated insulin sensitivity in gastrocnemius muscles of old compared to young rats has been found to be accompanied by less AMPK on its active phosphorylated form [85]. One-week treatment with the specific AMPK activator AICAR improved basal and insulin stimulated muscular glucose uptake in the old rats. Furthermore, the AICAR treatment also resulted in an alleviation of blunted expression of the insulin dependent glucose transporter GLUT4. Pharmacological activators of AMPK including metformin are widely used in the treatment of type-2 diabetes [86]. It is therefore feasible that a promoting impact of oxytocin on AMPK also directly exerts an insulin sensitizing effect on the skeletal muscles. In addition, the counteracting impact of oxytocin on sarcopenia [30] could probably be an important factor for the maintenance of skeletal muscles as an insulin responsive glucose clearing organ during aging. Possible routes for oxytocin to improve cardiovascular risk profile are outlined in Fig. 3.

Oxytocin protects pancreas and autonomous nerve function against age-associated deteriorations

The general anti-inflammatory effect of oxytocin which also encompasses a blunted response of pancreatic beta cells to metabolic stress [41] may have a preventive role against an impaired insulin function and type-2 diabetes late in life. Inappropriate pancreatic inflammation may lead to death of the beta-cells [41]. Insulin secretion has been found to be less affected by chemical oxidative stress after oxytocin administration in rats [80]. Pancreatic effects may therefore partly explain that an impaired glucose tolerance in old compared to young rats was improved by intraperitoneal injection of oxytocin during a 5-days period whereas no such effect was observed in the young rats [87]. In addition, the elevated levels of serum triglyceride and proinflammatory cytokines in the old rats were reduced by the oxytocin treatment to a level similar to what was seen in the young. Furthermore, following oxytocin treatment, homogenates of soleus muscle and epididymal fat from the old rats showed less inflammatory activity and oxidative stress assessed by malondialdehyde content.

The role of brain in the etiology of the metabolic syndrome and atherosclerosis cannot be overestimated. In this regard, a hyperactive sympathetic nervous system as a crucial factor has been well established for decades [88]. Sympathetic overactivity impairs endothelial function [89] which may lead to chronic hypertension and an increased level of vascular inflammation. Furthermore, it has also been reported to be statistically associated with dyslipidemia [90]. The paraventricular nucleus of the hypothalamus (PVN) appears to be an important part of the regulatory system governing the sympathetic tone in relation to blood pressure control [91]. Several studies support the idea that an elevated ROS production in the pre-autonomic PVN neurons induced by hyperactivity of their angiotensinergic innervation may result in a persistent augmented sympathetic tone. This may, in turn, promote the pathogenesis of the metabolic syndrome [92]. This idea is in line with the more general hypothesis that neuroinflammation particularly in the hypothalamus plays a pivotal role in the etiology of this condition [93].

It may be even more intriguing that hypothalamus beyond being the head quarter for body homeostasis also - by internal inflammatory processes - may represent the main regulator of general aging. In experiments with mice the inflammatory activity locally in the mediobasal hypothalamus was manipulated by up- or downregulation of NF-κB activity using an injected viral vector to express transcripts with promoting, respectively inhibiting effects on NF-κB [94]. Mice with downregulated hypothalamic NF-κB function had an increased lifespan and maintained their cognitive capacity, muscular size and strength, bone mass and dermal thickness better with age compared to the control mice. The opposite was the case for the NF-κB upregulated mice. In the same study, hypothalamic NF-κB activity was found gradually to increase with age accompanied by on increasing TNF-α production by the microglia cells in non-manipulated mice. The life extending effects of the downregulated hypothalamic inflammation was suggested to involve a protection of the gonadotropin-releasing hormone (GnRH) production which, in turn, may support restorative functions in the brain. Interestingly, GnRH might therefore be a signaling molecule which in parallel to oxytocin links reproduction with longevity.

An attenuating effect of oxytocin on the neuroinflammatory response to lipopolysaccharide (LPS) has been demonstrated. This was done both with isolated microglia cells pretreated with oxytocin and in frontal cortex tissue dissected from mice given oxytocin intranasally where LPS had been injected peritoneally [95]. Oxytocin may have a great potential to unfold its antioxidative and anti-inflammatory properties in the brain. At its production sites in paraventricular- and supraoptic nuclei oxytocinergic neurons are known to release oxytocin from their dendrites where it may travel through the intracellular fluid and reach neighboring parts of the hypothalamus [96]. Furthermore, the network of oxytocinergic projections to other areas of the brain [97] may be speculated also to have an anti-inflammatory capability.

Apart from counteracting neuroinflammation another cerebral role of oxytocin may be to influence the classic regulation of the autonomic nervous system. Oxytocinergic nerves project from PVN to different nuclei in the brainstem including the dorsal vagal complex (DVC) [98] which gives rise to vagal efferents innervating the thoracic and splanchnic areas including heart and pancreas. DVC also plays a crucial role in the brains control of glucose homeostasis [99] and blood pressure. Surprisingly, oxytocinergic innervation of DVC appears to be an integrated part in the baroreflex control of blood pressure [100]. Furthermore, oxytocin projection to the brainstem may participate in the general setting of the parasympathetic tone as demonstrated in experiments where rats were exposed to chronic intermittent hypoxia-hypercapnia (CIH/H) as a surrogate for obstructive sleep apnea [98]. Similar to what is seen in humans with sleep apnea the rats developed hypertension. This was accompanied with a reduced oxytocinergic outflow to the DVC. Furthermore, blood pressure was normalized during CIH/H if the decline in oxytocin release in the DVC was abolished by optogenetic activation of the PVN oxytocinergic neurons.

Maintaining a high oxytocinergic activity of the PVN may therefore alleviate damages of the heart inflicted by chronic hypertension. In a rat study, left ventricular overload was established by surgical *trans*-ascending aortic constriction [101]. After 8 weeks, the operated animals had developed fibrosis in their left ventricular walls and a reduced basal and stimulated contractility compared to the control group. These cardiac deteriorations could be mitigated by a chronic activation of the PVN oxytocinergic neurons which resulted in an elevated vagal stimulation of the heart.

In addition to the capacity to enhance the parasympathetic activity, oxytocin may also dampen the sympathetic tone by increasing the production of α_2-adrenoceptors in different parts of the brain [102]. α2-adrenoceptors acts inhibitory and an upregulation by oxytocin of these receptors particularly in locus coeruleus [103] may make the brain less sensitive to stressful stimuli. As locus coeruleus is the major site for cerebral noradrenergic output this could mean that its downregulation may lead to a reduced sympathetic responsiveness but, in fact, also an attenuated arousal of the hypothalamic–pituitary–adrenal (HPA) axis. An upregulation of the α2-adrenoceptors may therefore have a long-term protective effect against the detrimental effects of mental and physiological stress on blood pressure, metabolism and immune function. Treatment of rats with oxytocin subcutaneously or intracerebroventricularly during a 5-days period has been reported to have a blood pressure lowering effect which lasted more than week after the treatment was ceased [104]. Mechanisms of an increased hypothalamic oxytocinergic activity on cardiovascular risk profile are

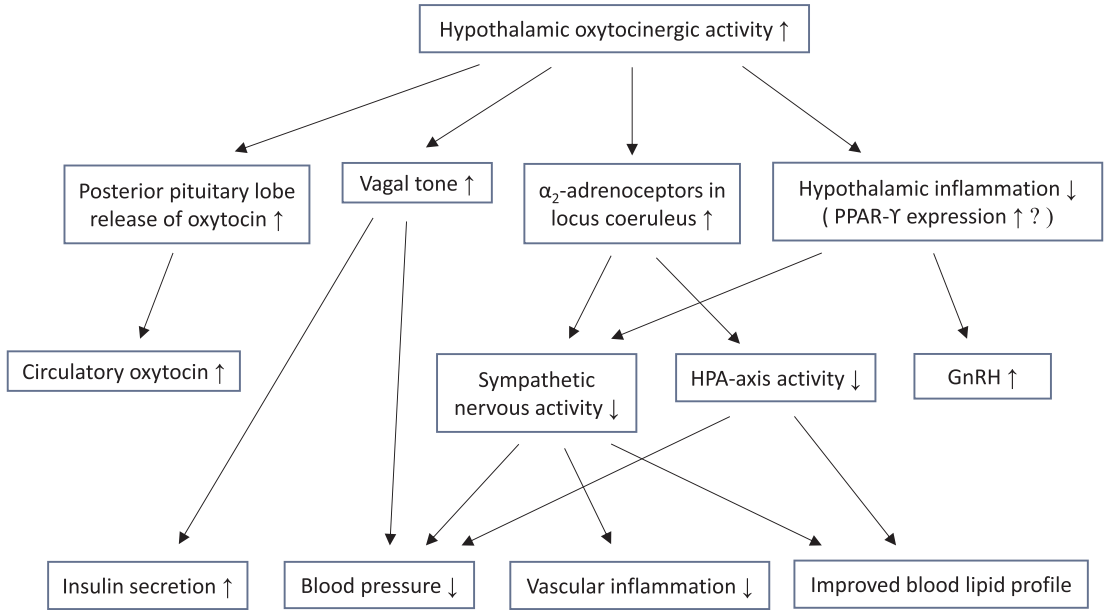

Fig. 4. Mechanisms of an increased hypothalamic oxytocinergic activity on cardiovascular risk profile.

outlined in Fig. 4.

Interactions with ANP

A stimulating effect of circulating oxytocin on cardiac release of atrial natriuretic peptide (ANP) has also been suggested to be involved in blood pressure regulation – particularly in relation to blood volume [105]. ANP has also been demonstrated to induce human white adipocytes to acquire brown adipocyte features including the expression of uncoupling protein 1 accompanied by an increased mitochondrial biogenesis and respiratory rate [106]. An enhanced ANP release may therefore contribute to the increased UCP1 expression in fat tissue samples and moderately reduced fat gain found in db/db mice when treated with oxytocin [107]. The so-called beige adipocytes residing within the white adipose tissue have been proposed to support energy and glucose homeostasis also in humans and to be a possible target for obesity treatment [108]. In general, the ability of oxytocin to stimulate ANP secretion may therefore make this peptide oxytocin's most important cardioprotective partner as ANP exhibits several properties counteracting cardio-vascular risk factors. Its different impacts can be exerted both by humoral routes and locally in the heart [109]. Oxytocin in the blood as well as oxytocin synthesized locally in the heart may delay atherosclerotic and cardiomyopathic processes otherwise accelerated by age, obesity and diabetes. This can be done by oxytocin alone or assisted by ANP [110].

The hypotesis evaluated: what does human studies indicate?

Experimental studies

Most of our knowledge about oxytocin is based on experiments with rodents which may differ to some degree from humans in their responsiveness of several organ systems to the peptide. Human research on oxytocin has mostly been focused on potential treatment effects for social disorders with the peptide administered nasally. In this context several different improvements had been reported from the labs but the applicability of oxytocin in the clinic for example to alleviate social deficits in autistic individuals calls for a lot of further field studies [111]. Nevertheless, these studies document that at least some brain areas can be reached with a therapeutic effect by exogenous oxytocin also in humans. However, very high doses of oxytocin may be required to achieve the central effects due to the poor nasal penetrance of the peptide. This would probably result in leakage to the general circulation in amounts having additional peripheral impacts [112]. This fact should also be considered in the interpretation of the few human studies addressing biological effects of oxytocin given by the nasal route.

Both central and peripheral effects of oxytocin might therefore have contributed to a reduced postprandial snack intake and a blunted glucose response to the breakfast after nasally administered oxytocin in men [113]. However, a reduction in ACTH and cortisol after oxytocin observed in the same study is rather likely only to be caused by central effects. In another study on men, indirect calorimetry revealed an increase in fasting fat oxidation and a correspondingly decrease in carbohydrate oxidation 30 min after nasally administered oxytocin [77] suggesting promotion of fat utilization in line with what is found in rodents [75]. The anorectic effect observed acutely with nasal oxytocin administration [77,113] seems to persist for weeks as a marked weight loss was reported in overweight subjects after 8 weeks treatment with self-administration of a nasal oxytocin spray prior to the three main meals and before bed [80]. A decline in total cholesterol and low-density lipoprotein following the 8 weeks oxytocin treatment was also seen. A capacity of oxytocin treatment to improve blood lipid in human is supported by an early study in young women where an intravenous bolus injection led to a decline in blood triglycerides. This was accompanied by increasing blood levels of non-esterified fatty acids and decreasing blood glucose [114].

Endogenous oxytocin may be mobilized with different positive effects by a variety of behaviors. An acute enforcement of the whole body antioxidative defense by breastfeeding is indicated by observations of an attenuated oxidative stress response of the mother to cesarean section if the infant was put to the breast immediately after the operation. Furthermore, post-surgical total oxidant status in serum was negatively correlated with the serum oxytocin level [115]. In addition, a reduced activity and responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis during breastfeeding has been reported by several studies [116] supporting the acute anti-stress effect of lactation. Interestingly, both breastfeeding and mechanical breast stimulation in non-lactating women has been reported to elicit an augmented plasma oxytocin accompanied by a decline in plasma ACTH and cortisol [117]. Repeated burst of oxytocin induced by recurrent episodes of lactation might potentiate the capacity for releasing oxytocin and the sensitivity to the peptide by the targeted cells. This potentiation may be hypothesized to

show a resilience which enables it to exert a cardioprotective impact for decades after the nursing period.

Apart from breastfeeding, sexual activities may also elicit robust bursts of oxytocin regularly. More than 4 times higher plasma levels of oxytocin have been reported in men at ejaculation compared to baseline in one study [118]. Plasma oxytocin concentrations had been reported to increase gradually during masturbation in both genders until it peaked at orgasm in men. In women, it continued to rise if a second orgasm could be achieved. Both baseline levels and the increase with masturbation was higher in women compared to men [119]. In another masturbation study, the relative increase in plasma oxytocin from baseline to orgasm was found to be positively correlated to the orgasmic pelvic muscle contraction both in men and women. In the multiorgasmic women, the relative oxytocin increase was also correlated to the subjective rating of the intensity of the orgasms [120]. The release of oxytocin during sex may be closely linked to the pleasure sensation as naloxone has been found to inhibit the rise in plasma oxytocin accompanied by a blunted feeling of pleasure during orgasm, despite that the rise in heart rate and blood pressure at orgasm was unaffected by naloxone [121]. This is in line with the observation of a lacking response of serum oxytocin to coitus in anorgasmic women [122]. It should be emphasized that elevations in the blood level of oxytocin may reflect a relatively much more pronounced increment of the oxytocinergic activity and impact in the brain.

Factors not directly involved in reproduction may also affect oxytocin activity. Oxytocin has been suggested to play an important role in the tranquilizing effect of non-sexual but pleasant tactile stimulation [123]. In rat experiments gentle stroking of their back has been seen to evoke an increased activity in oxytocinergic neurons in the hypothalamus [124] and massage-like stroking applied regularly was found to result in sustained higher levels of oxytocin in blood and periaquaductal grey matter [125]. In humans manually performed upper back massage has been reported to induce a modest enhancement in plasma oxytocin [126] and this method is recommended to reinforce breast feeding in some Asian and Middle eastern cultures [127]. In men, both manually and mechanically applied foot massage has been demonstrated to increase plasma oxytocin concentration [128]. However, in this study, the manual massage induced a more pronounced response and was claimed to be more pleasurable.

The sensation of love or other kind of affiliation may also evoke an oxytocin response as demonstrated during positive interactions between human and pets [129,130]. Finally, strenuous exercise may increase plasma concentration of oxytocin but studies in humans are inconsistent [131].

The epidemiological support of a cardioprotective effect of oxytocin

Cross-sectional studies associating oxytocin blood levels or other proxies of oxytocin activity to cardiac risk factors can not disclose causal relationships. Furthermore, research on genetic polymorphisms of the oxytocin receptor seems to be reserved for psychiatry whereas reports from prospective studies with direct assessment of baseline oxytocin parameters appears to be totally conspicuous by their absence but such investigations may be ongoing. What is left to provide any evidence in humans for the health protective potential of oxytocin are studies where activities known to elicit a robust oxytocin response are associated with different risk factors. In this case, the research pertaining to breastfeeding may be the most convincing.

Several retrospective studies indicate that breast feeding provides a long-lasting preventive effect against the development of cardio-vascular diseases. Postmenopausal women with a median age of 63 years who reported a lifetime history of more than 12 months of lactation had a lower prevalence of hypertension, diabetes, hyperlipidemia and cardiovascular disease even after adjusting for number of child births, present BMI, and sociodemographic and lifestyle variables compared to women who never had breastfed [132]. An independent inverse dose-response relationship between the total duration of their lactation history and the risk of presenting 3 or more characteristics of the metabolic syndrome were seen in women at their menopausal transition phase [133]. A risk reduction by lactation in the development of hypertension and cardio-vascular disease at 7 years post-partum follow-up has been detected both in groups of mothers who were normal weight/underweight and those who were overweight at the time of pregnancy [134]. Middle-aged mothers who had reported to having breast-fed each of their children for at least 3 mounts were found to be less likely to display coronary artery and aortic calcifications and showed less carotid plaque formations compered to mothers who never had breastfed [135]. These observations points to a protective effect of lactation against cardio-vascular diseases which last for several years. The involvement of epigenetic mechanisms could be hypothesized as the oxytocin system might be a target for epigenetic modulations. However, the involvement of other signal molecules associated with breastfeeding including prolactin cannot be excluded.

The possible protective impact of regular sexual engagements on the development of cardiovascular disease is less elucidated compared to that of breastfeeding. However, there are a few longitudinal studies which indicate a cardioprotective effect of sex. In a 25 year follow up study on volunteers examined at a medium age of 70 years, past enjoyment of intercourse in women and frequency of intercourse in men was found to be a predictor of longevity in a model, where possible confounding factors such as socio-economic status, tobacco use, health- and physical function ratings and satisfaction parameters were included [136]. In an investigation on middle-aged men, frequency of orgasms was negatively associated with all-cause mortality and tended to be negatively associated with coronary heart disease mortality at 10 years follow up also when data were adjusted for health- and socio-economic factors [137].

However, the causality of the observed associations between sexual parameters and cardiovascular disease are difficult to clarify. It is well established that erectile dysfunction often precedes coronary heart problems [138] and may be a marker of an impaired endothelial function. Concurrently, erectile dysfunction may reduce sexual activity. However, mechanisms related to oxytocin may also contribute to these findings. Positive effects of oxytocin release triggered by sexual pleasure may be similar to those hypothesized with breast feeding. One cross-sectional study on predicting factors for telomere length in various blood cells in young to middle aged women provides very interesting finding in this context. Different indices of health, stress, behavior and partner relationship quality were tested. Amongst these parameters recent sexual intimacy was the only variable which showed a highly significant association with telomere length in a multivariate correlation analysis [139]. High levels of oxytocin may have a defending effect against telomere truncation as suggested by a study where the protecting effect of social housing against telomere erosion in female rats could be abolished by the treatment with an oxytocin antagonist [140]. Telomeres appears to be particularly vulnerable to oxidative degradation [141] and a possible effect of oxytocin counteracting telomere attrition may be mediated by antioxidative effects.

The engagement in romantic relationships may rise the baseline plasma oxytocin level. Higher plasma levels of oxytocin have been detected in subjects of both genders being involved in courtships compared to singles [142]. Amongst couples, plasma oxytocin was found to be positively correlated with indices of mutual attachment [142] or experienced support [143] between the partners. In addition, affiliations of non-sexual, non-familial nature also appears to enhance the hormonal oxytocin level [144]. A cardioprotective impact of emotional bonds appears to be well established and supported by findings of an association between social isolation and risk of developing cardiovascular disease [145]. Pet ownership may relieve the detrimental effects of social isolation in some individuals by having a beneficial impact on risk factors including blood pressure, autonomic function and blood lipids [146]. In particular, dog ownership is associated with a

pronounced risk reduction in cardiovascular mortality [147]. The extent to which oxytocin is involved in the cardioprotective impact of social bonds in humans is difficult to clarify for ethical reasons.

Pharmacological aspects

Nonpharmacological approaches, including sexual pleasure and romantic relationships, may be insufficient fully to exploit the cardioprotective potential of oxytocin particularly during the later decades of life where the oxytocin function may have declined. In particular, it has been indicated that in female rats both the amount of plasma oxytocin and its receptor may go down with age as a consequence of a diminished estrogen stimulation [30]. In male rats, there have been reported a blunted oxytocin response to stress with age [148]. No investigations appear to have addressed the impact of advanced age on constitutive levels and responsiveness of oxytocin in humans. However, the increasing incidence of osteoporosis with age particularly in women may be one indication for an attenuated influence of oxytocin in elderly people.

Pharmacological treatment with oxytocin or oxytocin analogues could therefore be a possible preventive remedy in middle age and elderly patients exhibiting risk factors for cardiovascular disease. Traditionally, oxytocin is administered as nasal spray also when aiming at extracerebral locations such as breasts to promote milk let-down [149]. Applying this route, elevated plasma levels was observed until 90 min after a single nasal dose in men [150,151] whereas the concentration of oxytocin appeared to have a slower kinetic in the cerebrospinal fluid with increased readings only for the last sample at minute 75 [151].

Intra-nasal oxytocin administration for several weeks is very well tolerated in most people and in general, there are only very few reports of severe side effects with long-term oxytocin treatment including water intoxication [152]. One case of severe bradyarrhythmia has been reported with oxytocin infusion to induce labor [153] which may have been caused by excessive vagal stimulation. The impact of oxytocin on cardiac regulation should always be considered when the peptide is given to patients with particular heart conditions. Increasing the vagal tone has in most cases an anti-arrhythmogenic effect, however, frequent idiopathic slow rate-dependent premature ventricular contractions has been associated with high levels of parasympathetic activity [154]. Although not harmful, per se, this condition may be bothersome and reflect an imbalanced autonomic control. In general, it may be important to include cardiac monitoring regularly during long-term oxytocin treatment in patients displaying an abnormal ECG.

Central effects of oxytocin may be regarded as side effects if oxytocin is applied in the treatment of cardio-vascular disease. Despite that some cerebral effects may add to a cardioprotective effect the possible mental consequences of a chronically elevated cerebral level of oxytocin in mentally healthy humans are not sufficient elucidated. Sublingual or vaginal routes has been addressed as alternative methods for the administration of oxytocin. A protracted plasma oxytocin concentration curve has been reported with sublingual administration. However, the bioavailability of the dose was very poor and with a profound variability between subjects [155]. This was also the case in a study where oxytocin was given as a vaginal gel [156]. Moreover, the pharmacokinetic of plasma oxytocin is complicated and a two-compartment model may be required to give a satisfactory mathematical model [156]. Early kinetic studies should therefore be repeated with more accurate methods for the assessment of oxytocin [157] in different body compartments.

Biologically stable oxytocin analogues may have a prosperous future in the treatment of obesity and its comorbidities. An enhanced stability of oxytocin and similar molecules can be achieved when they are conjugated with lipids. Moreover, apart from the difficulties associated with the administration and fast degradation of native oxytocin, very high plasma concentrations of the peptide have been reported to elicit a transient pressor response in rats [158]. This is probably due to loss of oxytocin receptor selectivity resulting in actions on the vasopressin receptors. This might have been a motive for the development of oxytocin analogues with greater receptor selectivity than native oxytocin by replacing proline at position 7 with glycine. Such a lipid conjugated analogue was tested in diet induced obese mice [159]. Treatment with daily intraperitoneal injections of the analogue during a 2-week period resulted in a weight loss which was more marked than in mice given a corresponding treatment with native oxytocin. Furthermore, lean body mass was better conserved in mice treated with the oxytocin analogue. The high selectivity for the oxytocin receptor of the analogue was reflected by an absent acute hypertensive response to the treatment. However, transient hypertensive effects of native oxytocin may not be an issue in humans where an acute hypotensive effect rather is the major concern when high doses of oxytocin is administered. In the future, reports addressing possible beneficial effects of oxytocin analogues on inflammatory and tissue maintenance parameters would be very exciting.

The degradation of oxytocin results in different peptide fragments which may have their own specific activity. This has been demonstrated by mouse model showing social deficits corresponding to autism spectrum disorders [160]. The synthetic oxytocin receptor agonists TC-OT-39 and carbetocin failed to exert any prosocial effects whereas some of the oxytocin fragments did. Furthermore, findings that long-term analgesic and hypotensive effects of oxytocin was insensitive to the oxytocin receptor antagonist atociban supports that non-conventional route of oxytocin signaling possibly involving particular degradation products may exist [161]. Some of the biological effects of native oxytocin may therefore be absent when applying oxytocin analogues due to a failed production of metabolites. This could be a matter of concern also if such analogs are employed for the prevention and treatment of cardiovascular disease. In general, such unexpected effects specific for native oxytocin may encourage the research for ways to potentiate the brains own release of oxytocin beyond what can be achieved by behavioral approaches. In this context, microbiotic interventions may turn out to be very exiting [37].

Consequences and discussion

In this article we have presented some evidence that the oxytocin system may constitute an important target for the prevention and possibly treatment of cardiovascular disease. Oxytocin may have several avenues at hand to improve cardiovascular health. Atherosclerotic formations may be counteracted by antioxidative and anti-inflammatory effects on the endothelia. Central stress reactions may be dampened with a reduced activity of the sympathetic nervous system and HPA axis while the parasympathetic tone is enhanced. By acting on pancreas and skeletal muscles insulin function can be potentiated. By stimulating repair and survival mechanisms not at least of the stem cells the integrity of the myocardium and vascular tissue may be defended. By promoting restoration of the mitochondria, cellular energy supply is preserved. This would also be the case for cardiomyocytes sustaining the contractibility of the heart.

In the future, more knowledge about oxytocin may lead to a conceptual change where a behavior promoting oxytocin release is adopted as part of a healthy lifestyle. It is needless to say that the establishment of more and better social bonds is problematic to include in the public health recommendations. It may be slightly less sensitive to recommend frequent sexual and tactile pleasures in parallel to regular physical activity as a health strategy particularly if future research may indicate effects which are similar to those of breast feeding.

With regard to the pharmaceutical aspects, oxytocin analogues may be developed which offer a safe treatment regimen and prove a great efficacy for the prevention of cardiovascular disease (and postponement of other degenerative maladies). The threshold for prescription of such agents may become very low and possibly an age above 50 years might

be a sufficient indication. Meanwhile, indispensable requests prevail for preclinical and clinical investigations pertaining to the potential of targeting the oxytocin receptor in the battle against heart problems. Initially one option may be studies applying nasal administration of native oxytocin for long term treatment of both men and women who show risk factors for cardiovascular disease. Would their blood lipid profile, insulin function, heart rate variability or body fat distribution be improved?

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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