

# Exocrine pancreatic insufficient pigs as an animal model to study brain structure and function during pancreatic insufficiency in humans: Effect of pancreatic-like enzyme replacement therapy

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## Introduction

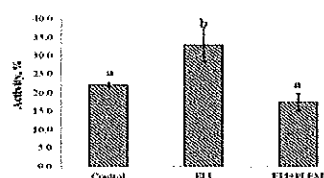
Acute and chronic pancreatic insufficiency in humans is often associated with marked neurological alterations related to cognitive and sensory motor function. However, no animal model permitting brain studies under these conditions is available (1). A model of exocrine pancreatic insufficiency in the young pig (EPI pigs) has been developed and is well established; these animals do not grow and have very poor fat and protein absorption (2,3,4,5). - The aim was to study changes in neurospecific protein distribution, hippocampal morphology and behaviour of EPI pigs, and to study if replacement therapy with pancreatic-like enzymes of microbial origin (PLEM) can alleviate these changes.

## Materials and Methods

Twelve castrated male piglets 6±2 wks of age and 11.3±2 kg at surgery (pancreatic duct ligation [2]) were randomized into 3 groups: Control (n=4) intact pigs; EPI pigs (n=4), and PLEM pigs (n=4) where EPI pigs received pancreatic-like enzymes of microbial origin in their diet (5). The pigs were fed a cereal based feed for young growing pigs (Lantmannen, Sweden) enriched with ca. 15% extra fat twice daily for three weeks. The treated pigs received 4 PLEM capsules at each meal. Each capsule contained 57.4 mg enzyme mix: 30,000 lipase U, 20,000 protease U, 3,000 amylase U, using commercially available enzymes.

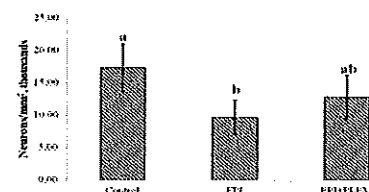
Using standard methods, animal behaviour and activity were evaluated on 2 consecutive days at the end of the study. The pigs were then sacrificed and the brain removed and sampled for biochemical analyses and the evaluation of morphology. Statistical analyses using Statistica 7 (StatSoft, USA) were carried out.

## Results



**Figure 1.** Changes in pig activity (% obs. time, n=12) The EPI group showed significantly ( $p \leq 0.01$ ) more activity than the control (intact) (Fig. 1), and the PLEM pigs, respectively. A significant reduction in the levels of glial filament protein (GFAP) and calcium binding protein, S100b, was found in the hippocampus (the CA1 area) of EPI pigs and slightly higher levels of soluble

GFAP. PLEM treated EPI pigs showed levels of these and other biochemical parameters (e.g., neural cell adhesion molecule [NCAM]) similar to that of the control pigs. The amount of hippocampal neurons were significantly ( $p \leq 0.05$ ) lower in EPI pigs than the controls, and also lower than those receiving PLEM (Fig. 2).



**Figure 2.** No. neurons per 1 mm<sup>2</sup> in the CA1 hippocampal area in the pigs (n=12)

## Conclusions and Discussion

The present study demonstrates that EPI may result in the reduction of the number of pyramidal neurons in pigs' hippocampus, reduction in the NCAM level, and a pathological increase in animal activity. These negative effects in pigs can be significantly reduced by pancreatic-like enzymatic replacement therapy. Thus this animal model may be relevant with respect to studying the clinical use of pancreatic enzymes under EPI conditions in humans.

## Acknowledgments

SGPlus – Sweden

## References

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