Selective dynorphin and nociceptin system alterations in the alpha-galactosidase A deficient mouse model of Fabry disease

1)Rullo L. 2)Caputi FF. 3)Romualdi P. 4)Candelletti S.

University of Bologna

Fabry disease (FD) is a multi-system disorder due to enzyme alpha-galactosidase A (α-Gal A) deficiency and progressive lysosomal deposition of globotriaosylceramide (GL-3) in cells throughout the body (Schiffmann, 2009). The classic form, occurring in males with less than 1% α-Gal A enzyme activity, usually has its onset in childhood or adolescence. Heterozygous females typically have milder symptoms at a later age of onset than males. The most characteristic neurological manifestation is a latching painful neuropathy affecting mainly the feet, legs and hands (acroparesthesia) (Toyooka, 2011). Specifically, it has been demonstrated that FD patients show reduced intraepidermal nerve fiber density and impaired thermal perception (Dutsch et al. 2002; Biegstraaten et al. 2011). In addition, it has been demonstrated that the α-Gal A(-/0) hemizygous male mice (FD mouse model) present molecular and structural alterations in pain sensation such as heat/cold-hyperalgesia and mechano-hyperalgesia (Lakoma et al. 2016). In the present study, we explored the involvement of the DYN-KOP and the pN/OFQ-NOP systems since they are known as the major systems involved in pain control (Mika et al. 2011). The gene expression was assessed by Real-Time PCR using the Delta-Delta Ct (DDCt) method in selected brain regions of 4 month wild type and α-Gal A(-/0) hemizygous male mice (n=6/group) (all mice were kindly provided by Dr. Caprini).

The qPCR analysis revealed a marked increase of pDYN (1.55 ± 0.10 vs wild type 1.00 ± 0.09) and KOP (1.25 ± 0.04 vs wild type 1.00 ± 0.09) gene expression as well as the up-regulation of NOP mRNA levels (1.37 ± 0.05 vs wild type 1.00 ± 0.13) in the thalamus (TH) of FD mice; no changes of pN/OFQ gene expression were reported. Conversely, in the PFCx the gene expression analysis showed a significant down-regulation of pDYN (0.65 ± 0.04 vs wild type 1.00 ± 0.12) and KOP genes (0.62 ± 0.08 vs wild type 1.00 ± 0.07). The pN/OFQ and NOP genes did not shown significant changes between mice group. A similar reduction of pDYN-KOP genes (pDYN: 0.54 ± 0.12 vs wild type 1.00 ± 0.07, KOP: 0.68 ± 0.08 vs wild type 1.00 ± 0.11, respectively) was observed in the AMY of FD. In this region gene expression data also showed a selective up-regulation of pN/OFQ (1.47 ± 0.08 vs 1.00 ± 0.06). In the HIPPO the analysis revealed a significant decrease of pDYN mRNA levels (0.58 ± 0.09 vs wild type 1.00 ± 0.12) and a strong up-regulation of its KOP receptor (2.50 ± 0.38 vs wild type 1.00 ± 0.09). No changes of pN/OFQ and NOP genes were reported in the HIPPO. Data here reported indicate for the first time that specific alterations of opioid system occur in selected brain regions of FD murine model. Moreover, the well known involvement of DYN-KOP and pN/OFQ-NOP systems in nociceptive transmission and in the affective components of pain, might somehow underlie peculiar somatosensory manifestations of FD.

References:

Schiffmann R. (2009) Pharmacol. Ther. 122:65-77.

Toyooka K. (2011) Current Opinion in Neurology 24:463-468.

Dutsch M. et al. (2002) Journal of Clinical Neurophysiology 19:575-586.

Biegstraaten M. et al. (2011) European Journal of Pain 15:822-829.

Lakoma et al. (2016) PLoS One. 9:e108641.

Mika J. et al. (2011) Neuropeptides 45:247-61.