GAMMA HYDROXYBUTIRATE (GHB) MODULATES NPY – Y1 RECEPTOR SIGNALLING IN THE AMYGDALA OF TRANSGENIC MICE THROUGH GABAB RECEPTOR IN A NEUROSTEROIDS INDEPENDENT MANNER.

Mele P.[a], Serra M.[b,c,d], Pisu M.G.[b,d], Eva C. [a], Biggio G [b,c,d]

[a] Dep. Of Anatomy, Pharmacology and Forensic Medicine, Section of Pharmacology, University of Turin, Italy. [b] Dep. of Experimental Biology, Sec. of Neuroscience, University of Cagliari, Cagliari, Italy. [c] Center of Excellence for the Neurobiology of Dependence, University of Cagliari, Cagliari, Italy. [d] C.N.R. Institute of Neuroscience, Cagliari, Italy

Neuropeptide Y (NPY) is one of the most abundant peptides in the CNS.. The activation of the Y1R for NPY elicits behavioral effects that are indistinguishable from those induced by activation of $GABA_A$ receptors and NPY-Y1R signalling in the amygdala is also implicated in the neurobiological responses to ethanol intake and discontinuation. Studies performed in our and others laboratories have demonstrated that NPY coexist with GABA within the same neurons and that GABA-NPY interaction plays an important role in regulation of emotional behavior and neuronal excitability. Furthermore we have shown that an increased production of neuroactive steroids, potent positive modulators of GABAA receptor, is an important physiological determinant of NPY-Y_1R transmission and that the ability of ethanol discontinuation to affect NPY-Y_1R transmission in the amygdala depends on fluctuations in the brain concentration of the neuroactive steroid e (3α,5α-TH PROG).
Gamma-hydroxybutirate (GHB) is a natural compound, effective in the pharmacotherapy of alcohol dependence while, on the other side, may have addictive properties leading to abuse. GHB, like ethanol, increases brain concentrations of neuroactive steroids and can also acts at a specific neuronal receptors (GHB receptors), which probably mediates many of its effects. By using *Y_1R/LacZ* transgenic mice, which harbor the murine Y_1R gene promoter linked to a *lacZ* reporter gene, we have now investigated whether NPY might represent one of the targets of the pharmacological action of GHB. To do this we treated Y1R/LacZ transgenic mice with agonists (GHB, baclofen) and antagonists (SCH50911, NCS382) versus both GABAB and GHB receptor or with finasteride to clarify which mechanism may influence NPY/Y1 neurotransmission. The treatment with GHB (150-600 mg/kg, i.p.) increased the level of NPY i.r. and concomitantly decreased *Y_1R/LacZ* transgene expression in both the medial and central amygdala, in a dose dependent manner. The effect of GHB on both NPY i.r. and *Y_1R/LacZ* transgene expression was mimicked by the GABAB receptor agonist baclofen (6 mg/kg, i.p.) and was blocked by the GABAB receptor antagonist SCH50911 (50 mg/Kg, i.p.) Conversely, pre-treatment with either NCS382 (50 mg/Kg, i.p.), a GHB receptor antagonist, or finasteride, which prevent the increase in the cerebrocortical concentration of 3α,5α-TH PROG normally apparent after GHB administration, failed to inhibit the effect of GHB. These data suggest that GHB may affect NPY-Y_1R signalling in the amygdala. This effect is mediated by GABAB receptor activation and is independent on fluctuation of neurosteroids concentration.