Summary

Recently a great amount of attention is beginning to be directed towards the role of the ORXergic system in several biological processes such as feeding, energy balance, sleep-wake cycle and motor behavior in Rodents. Studies have already shown that several ORXergic activities of its two major peptides (ORX-A/B) are modulated by cross-talking mechanisms with other neurotransmitter systems such as GABA and Glu. It is important to point out that some α $GABA_A$ neuroreceptor subunits are not only involved with the modulation of anxiogenic/anxiolytic reactions but are also capable of modifying ORXergic transcriptional activities and consequently altering neuronal processes such as synaptic plasticity. In this study the effects of ORXergic and GABA/Gluergic agonists were evaluated on the hamster *Mesocricetus auratus*, a facultative hibernator, through their administration into the basolateral and the central nucleus of the amygdala by icv injections. A first behavioral result pointed to, aside a direct blocking role on feeding behaviors by the ORXergic-GABAergic interaction within both the basolateral and central nucleus of the amygdala, modified drinking rhythms by only the latter nucleus. Conversely the Gluergic effect proved to be of a synergic type on both ORXergic-dependent feeding and drinking activities. Interestingly it seemed that the α_1 $GABA_A$ receptor subunit together with ORX promoted a great increase of food-intake in the hibernating hamster despite no evident weight increase, which might be correlated very likely due to a net rise of energy-metabolism. In addition icv injection of central nucleus with ORX-A/B ± the agonist of α_2 $GABA_A$ receptor subunit (flunitrazepam) allowed me to suggest a greater anxiogenic effect of ORX-B as shown by our hibernating rodent model spending more time in the closed arm chamber of the elevated plus-maze as well as in the dark box of the light-dark testing apparatus while these effects were suppressed when animals was treated with α_2 agonist.

From *in situ* hybridization expression levels of ORX2R site it appeared that both subunits and especially α_1 reduced the quantities of this ORXergic receptor site in prevalently hypothalamic and amygdalar areas. Conversely, the Gluergic agonist (NMDA) exerted an up-regulating effect on ORX2R levels in predominantly limbic and cortical regions. In this context, transcriptional modifications could prove to be the initial molecular factors considered essential for excitatory phenomena through highly evolved feedback actions aimed at maintaining in equilibrium excitatory and inhibitory neuronal mechanisms. This type of interaction may turn out to be very crucial for hibernation especially since the activity of both neuroreceptor systems are capable of exerting protective actions and thus assuring the execution of all the different hibernating phases

especially the arousal state that exhibits ischemic-like events. Moreover at the cellular level, it seemed that ORXergic effects were linked to evident argyrophilic reaction (neurodegeneration phenomena) including altered cell membrane and loss of cytoplasmic architecture of hypothalamic and mesencephalic neuronal fields, which may turn out to be together altered ORX2R expression levels eliciting elements of anxiogenic/anxiolytic above all for α_2- dependent activities. Overall it is tempting on the basis of these results to suggest a neuroprotective role of α_2 $GABA_A$ inhibitory signals against the over-excitatory ORX-dependent neurodegenerative reactions and consequently abnormal anxiety-like behavior that may prove to be therapeutically useful for ORX-dependent sleeping and neurodegenerative disorders.