LYMNAEA STAGNALIS AS A NEW MODEL FOR TRANSLATIONAL MEDICINE

1)Benatti C. 2)Colliva C. 3)Alboni S. 4)Brunello N. 5)Tascedda F.

University of Modena and Reggio Emilia

Neuropsychiatric and neurodegenerative disorders are of complex aetiology, to help identify and study the molecular and physiological mechanisms involved in their aetiopathogenesis or in the response to effective treatments, numerous animal models have been developed in a variety of species. Small mammals (i.e. rats and mice) are usually the model of choice, but this approach may not be always effective and is accompanied by many ethical and economical drawbacks. On the other hand, invertebrates, thanks to their relatively simple nervous systems and to the latest technique in genome sequencing and manipulation, are becoming a useful tool for translational medicine and drug elucidation (Tascedda et al., 2015). In particular, the pond snail Lymnaea Stagnalis (LS), an aquatic pulmonate gastropod with a CNS consisting of ≈20,000 neurons organized in a ring of interconnected ganglia, has proven to be an extremely useful and accessible model to study fundamental aspects of CNS function such as synaptic plasticity and associative memory.

The serotonin (5HT) system represents an ideal target to be studied in LS, in fact it is highly conserved in both vertebrates and invertebrates, modulates a wide range of behaviours (including sleep, feeding, and mood), and numerous evidence supports a biological link between neuropsychiatric disorders and the serotonin pathway. So far, the molecular machinery governing 5HT signalling that has been identified in the ganglia of LS are: tryptophan hydroxylase (LymTPH), the enzyme catalysing the first and rate limiting step in the biosynthesis of serotonin, different subtypes of 5HT receptors (Lym5HT1 and Lym5HT2), and LymSERT, the snail homologue of mammalian SERT, that removes serotonin from the synaptic cleft. In LS, analogue of CREB (LymCREB1) and NPY (LymNPY) were also cloned, CREB is known to regulate the downstream expression of cAMP-inducible genes including NPY, and both targets are proposed to be involved in anxiety and neuropsychiatric disorders.

Our aim was to evaluate the effect of serotonergic stimulation on the expression levels of these targets in the CNS of LS. In doing so, adult snails were treated chronically (48 hrs) or acutely (6 hrs) with 5-hydroxy trypthophan (5HTP, 1mM), the immediate precursor of serotonin, with fluoxetine (FLX, 1µM), a selective serotonin reuptake inhibitor, or with a combination of the two compounds. The central ring ganglia were dissected, RNA extracted, retrotranscripted and used for q-PCR gene expression analysis.

Transcription was strongly induced following a chronic, but not an acute, exposure to 5HTP in the ganglia of LS. In particular, LymCREB1 was increased in snails receiving 5-hydroxy tryptophan for 48 hrs with respect to the control group, while we observed a significant decrease following a 6hrs 5HTP exposure. Interestingly, the transcriptional induction was inhibited when snails were exposed to both 5HTP and FLX (while FLX alone did not affect mRNA levels of the evaluated targets), suggesting a role for SERT in mediating the effect of 5-hydroxy tryptophan.

These data suggest that Lymnaea Stagnalis is ideally suited to unravel the complexity of the serotonin signalling pathway and may represent a good model to provide new insights on how serotonin can modulate cognitive functions and its role in neuropsychiatric and neurodegenerative disorders

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