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LETTER TO EDITOR

Lymnaea stagnalis as model of neuropsychiatric disorders

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To the Editor

This paper describes the advantages of adopting a molluscan model for studying the biological basis of some central nervous system pathologies affecting humans. In particular, I will focus on the freshwater snail *Lymnaea stagnalis*, which is already the subject of electrophysiological studies related to learning and memory, as well as ecotoxicological studies (Il-Han *et al.*, 2010; Bavan *et al.*, 2012; Ivashkin *et al.*, 2015; Benatti *et al.*, 2017; Ito *et al.*, 2017).

Understanding psychiatric and neurological disorders is a major medical and scientific challenge. These pathologies are extremely widespread and contribute in an important way to the high cost of public health (Nestler *et al.*, 2010; Tascedda *et al.*, 2015; Kaiser *et al.*, 2015).

Unfortunately, the developing or mature human brain are not open to direct molecular observation, and experimental manipulations are clearly not ethical. This makes it necessary and urgent to develop new and reliable animal models for the study of brain disorders.

While the research community has accepted the value of rodent models for the study of human pathology and treatment, there is less awareness of the utility of other small vertebrate and invertebrate animal models.

However, in recent years, the neuroscientists are increasingly turning to smaller, non-rodent models to understand molecular physiopathological mechanisms related to neurological or psychiatric disorders. Although they can never replace clinical research, these species offer flexible genetic tools that can be useful to validate the function of specific genes, or their role in more complex functions. Although, animal models, of any origin, size or complexity, can never summarize the full phenotype of a human clinical disorder, in particular neuropsychiatric ones, different small animals, such as, worms, flies, bees and fish offer new important and innovative tools for the neuroscientist. (Burne *et al.*, 2011; Curran *et al.*, 2012; Tascedda *et al.*, 2015).

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Indeed, by using a range of models of different complexity, together with a number of different experimental approaches, researchers can divide complex phenotypes into simpler neurobiological correlates of clinical syndromes (Nestler *et al.*, 2010).

As mentioned above, normally, for these studies, rats and mice have been used (Vinet *et al.*, 2003; Vinet *et al.*, 2004; Blom *et al.*, 2006; Alboni *et al.*, 2011; Benatti *et al.*, 2011), but this approach may not be always effective and is accompanied by many ethical and economical problems (Tascedda *et al.*, 2015). Many researchers have attempted to solve the problem by using *in vitro* cell systems (Alboni *et al.*; 2013, 2014; Caraci *et al.*, 2016) that have many important advantages (Tascedda *et al.*, 2015). Unfortunately, the results are often inconclusive and fail to elucidate the basis of disease (Alberts, 2010).

Given of these considerations, the need to identify alternative and reliable models that have fewer ethical restrictions is both important and urgent.

Invertebrates, thanks to their relatively simple nervous system structure are fast becoming a useful tool for the study of neuronal physiology and for better disease process characterization (Kaang *et al.*, 1993; Ottaviani *et al.*, 2013; Tascedda *et al.*, 2015).

Above all, molluscan gastropods, such as *Aplysia*, *Hermissenda*, *Limax*, and so forth, have been widely recognized as useful animals with which to study the molecular and cellular mechanisms underlying complex human pathologies such as neurological and psychiatric disorders (Kandel *et al.*, 1965; Gelperin 1975; Nestler *et al.*, 2010; Burne *et al.*, 2011).

Furthermore, numerous studies suggest that the pond snail *L. stagnalis* could be an innovative useful model in genetic and translational research for the study of the molecular basis of human brain diseases and for the development of new therapeutic strategies (Tascedda *et al.*, 2015, Ito *et al.*, 2017, Benatti *et al.*, 2017).

L. stagnalis, an aquatic pulmonate gastropod with a central nervous system (CNS) consisting of ≈20,000 neurons organized in a ring of interconnected ganglia, has proven to be an extremely interesting and accessible model to study

fundamental aspects of CNS function such as synaptic plasticity and associative memory (Sadamoto *et al.*, 2004, 2010; Ito *et al.*, 2017). Compared to *D. melanogaster* and *C. elegans*, *Lymnaea* has many benefits due to the large size of its neurons, results from electrophysiological studies, and its already characterized neuronal circuit (Andrianov *et al.*, 2015). *Lymnaea* also offers the possibility of performing behavioral tests [Ito *et al.*, 2017]. More importantly, while *D. melanogaster* and *C. elegans* have a life cycle of 2 - 3 weeks, *Lymnaea* has an average life span of 9 - 12 months. This last factor becomes particularly interesting and useful in studies on chronic human pathologies, especially neurodegenerative diseases such as Alzheimer's, Parkinson's or chronic psychiatric diseases such as major depression, schizophrenia or bipolar disorder.

In this context, *L. stagnalis* offers, to the neuroscientist involved in translational medicine, a powerful new tool to study neuropsychiatric diseases and allow the identification of new molecular targets for the development of innovative therapeutic strategies.

Using an interdisciplinary approach, studying the appropriate animal model, passing from the more simple ones to the most complex, while combining different methods and expertise that include fields as evolution, ecology, and life history theory with physiology, pathology, neuroscience, genetics, molecular biology, and ultimately behaviour it will be possible to open new frontiers to understand and cure brain illnesses.

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