MedicalXpress

Aggressive flies: A powerful new model for neuropsychiatric disorders

June 7 2017

Alterations in social behaviour, including aggression, are associated with a number of neuropsychiatric disorders such as schizophrenia and bipolar disorder. Along with DiGeorge syndrome and velo-cardio-facial syndrome, these disorders are linked to mutations in the proline dehydrogenase gene PRODH, which is situated in a region known as 22q11 on chromosome 22. The PRODH protein is localised on the inner membrane of mitochondria and known to be involved in proline catabolism; however, the exact mechanism by which PRODH and altered proline metabolism contribute to neuropsychiatric disorders is not well understood. Researchers have previously used mouse models to investigate the role of PRODH in schizophrenia and other conditions associated with 22q11 mutations. Now, a team from the University of Leuven in Belgium and the University of Bristol in the UK have published new research in *Disease Models & Mechanisms* (DMM) providing insights into the cellular mechanisms that link PRODH defects and behavioural disorders using a new fruit fly (*Drosophila melanogaster*) model.

The primary goal of the study was to determine whether the social behaviour of fruit flies, measured in this case as aggression, could be used as a model for neuropsychiatric disorders in humans. In particular, lead investigator Patrick Callaerts and his team wanted to use the fly model to uncover the role of proline metabolism. The study revealed that SlgA - the fly protein most similar to human PRODH - is broadly found in the brain of adult flies. However, abnormal behaviour, namely increased aggression, was only induced when a specific part of the brain,

the lateral neurons ventral (LNv), was subjected to manipulated levels of SlgA and treatment with human PRODH. These results suggest that there are cell-type specific contributions to distinct behaviours, and that proline metabolism needs to be precisely regulated to drive normal behaviour. The research team also uncovered that these behavioural changes might at least partly be mediated by disruptions to mitochondrial function and morphology.

It's not about time

Cells in the LNv, also known as 'clock neurons', have previously been identified as crucial pacemaker neurons in the regulation of circadian rhythmicity. However, although defects in body clock rhythms and sleep problems are associated with neuropsychiatric disorders, Callaerts and his team found that SlgA disruption did not affect circadian rhythms in their model flies, indicating that the *Drosophila* clock neurons have additional, unknown functions. Callaerts says, "Our results show that they also have a role in regulating aggression that is separate from their role in circadian rhythmicity."

The value of multiple models

Weighing up the advantages of flies as a model organism over mice in the study of neuropsychiatric disorders, Callaerts explains that fruit flies have an extensive genetic toolkit - the genetic techniques used by scientists for analysis of gene function and genetic interactions - and that these tools can yield results faster than in mice. Genes identified in the fly models can then in turn be validated in mouse models. He adds, "It is at all times valuable to establish multiple models. The complementarity of different models should enable us to get good insight into the significance of particular genes for normal behaviour and by extension for the genetic causes of abnormal behaviour."

Defining alternative treatments

The group plans to further define the value and potential of fruit flies as a model for psychiatric disorders. The effectiveness of current therapeutics for neuropsychiatric disorders is not uniform, and is influenced by genetic background. To address this, Callaerts and his team are exploring the role of the genome in the observed variation in responses to drugs used in the treatment of bipolar disorder. In another project, the team is investigating the cellular mechanisms that drive abnormal behaviour in the fly, again using aggression as model behaviour. Reflecting on the importance of their research for individuals with neuropsychiatric disorders, Callaerts says, "Once we have demonstrated the direct relevance of our *Drosophila* models for psychiatric disorders, we aim to pursue drug screens. In that sense our work may contribute to defining alternative treatment options."

More information: Liesbeth Zwarts et al, SlgA, the homologue of the human schizophrenia associated PRODH gene, acts in clock neurons to regulateaggression, *Disease Models & Mechanisms* (2017). DOI: 10.1242/dmm.027151

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