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# The genetics of reward behaviour

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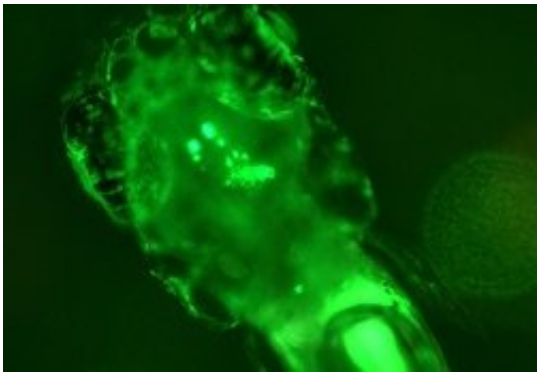

Credit: Petronella Kettunen

Reward systems lie at the very heart of human behaviour – from eating tasty food to falling in love. Researchers with the EU project have turned to the zebrafish for details of the molecular basis that is also behind the development of many neuropsychological illnesses.

The forebrain dopaminergic (DA) system has many roles in brain function, including working memory and is a key determinant of Parkinson's disease development. It is also important in some neuropsychological conditions, and commonly abused drugs, such as alcohol, exert influence through this so-called reward DA system.

Working with the emerging technologies of in vivo imaging, optogenetics and transgenic techniques, the FISHDOPA team investigated the complex DA neural network in Danio rerio, the well-

known model zebrafish.

## Genes involved in learning in reward behaviour

Prof. Petronella Kettunen, FISHDOPA project coordinator outlines how the researchers analysed the brain regions and signalling pathways involved when the DA system kicks in and results in modified behaviour patterns. "Results showed consistent activation of DA neuronal populations in two forebrain areas, called the dorsal (Vd) and the ventral (Vv) part of the ventral telencephalon," explains Prof. Kettunen.

Using laser capture microscopy they then collected mRNA samples from the Vd and Vv regions and after next-generation sequencing the team could see what genes were expressed during learning of reward behaviour. "Our preliminary bioinformatics analysis indicates that while the Vd shows an upregulation of genes associated with dopamine signalling before reward learning, the Vv shows upregulation of genes associated with learning after reward learning," outlines Prof. Kettunen. This clearly implies that Vd is important for reward processing and the Vv for reward learning.

## Significance of FISHDOPA results for learning and addiction

FISHDOPA has developed a behavioural paradigm to study reward and learning to understand the molecular mechanisms underlying this behaviour. Moreover, use of laser capture microscopy to cut out and sample small brain regions from sectioned adult zebrafish brain, extraction of mRNA and next-generation sequencing on the samples is a new protocol.

A first in the reward behaviour field, FISHDOPA has shown that it is

possible to use both larva and adult zebrafish. This opens up future applications and research in the important areas of neurotransmission, learning and addiction. "What is most important is that we have identified different areas of the brain involved in the reward system," stresses Prof. Kettunen. "Our data indicate that different brain regions and signalling pathways are recruited during different aspects of the behaviour."

## Clearing the hurdles in behavioural research challenges

Being at the forefront of research in the reward-related behaviour field, there were many challenges tackled by the FISHDOPA team. "Many methods/tools were lacking and limited information was available regarding, for example, brain function in the fish. Therefore, we had to develop or refine a large portion of the methods used, including the behavioural tests, evaluation of antibodies and available transgenic fish," explains Prof. Kettunen.

Another challenge was to manipulate and follow the delicate and complex behaviour involved in learning in freely moving zebrafish, and to investigate at what time-point during development that the reward behaviour is developing in the larvae. As Prof. Kettunen points out, "The older the animals get, the more restricted you are as a scientist with the available technology for in vivo imaging, for example."

## Next steps in the path to application of DA system in the clinic

A future focus will be to study the function of the new genes discovered during project research and extend the investigations to human gene cascades. "In addition to dopamine, other signalling pathways involved in

reward learning can be investigated and this can be tested pharmacologically or genetically in future experiments," points out Prof. Kettunen.

Dysregulation of the dopaminergic system is associated with several psychiatric and neurological diseases and syndromes, such as Parkinson's disease, Alzheimer's disease, ADHD and depression. In addition, dopamine has a pivotal role in addiction. As Prof. Kettunen concludes, "We still lack efficient and safe treatments for many of these disorders related to dopaminergic dysfunction and new tools developed in FISHDOPA could be of great help in the process of finding new cures."

Provided by CORDIS

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