# Social Behavioral Disorders: A Discovery with Impact on Therapeutic Strategies

**Prof. Claudia Bagni's team at UNIL's Department of Fundamental Neurosciences has identified a new mechanism that could have an impact on the treatment of neurological disorders such as autism or schizophrenia. This would involve targeting the Aralar protein in the brain, which tunes the communication between certain neurons in response to the neurons' energy consumption. This discovery is published in the March 19, 2020 edition of the journal *Cell*.**

The brain uses 20% of the body's energy. This energy is produced by the mitochondria, microscopic intracellular structures that provide the fuel necessary for cell activity. For many processes, neurons depend on the proper functioning of these small structures. Autism is a neurodevelopmental disorder that is characterized by maladaptive social behavior and carries a severe cost for the lives of the patients and their families. Autism affects 1-2% of children, of which 5-8% are explained by defects in the mitochondria.

In the scientific article published on 19 March 2020 in the journal *Cell*, the team of Prof. Claudia Bagni, Director of the Department of Fundamental Neurosciences (DNF) of the Faculty of Biology and Medicine at UNIL, discovered how mitochondrial dysfunction/s can affect social interactions.
Professor Bagni and her team have long been interested in studying the molecular, cellular and behavioral basis of autism (ASD), Fragile X syndrome and schizophrenia (SCZ). In this research project they could now show that the mitochondria can sequester the neurotransmitter gamma-aminobutyric acid (GABA), which changes the communication between neurons and alters social behaviour. The culprit for this sequestration? Excessive activity of the Aralar molecule. Countering its action could therefore improve the lives of individuals with those deficits. To make this discovery, Prof. Bagni's team had the privilege of collaborating with international institutions in the United States, the Netherlands, Germany, France, Belgium, the United Kingdom and Italy, sharing knowledge and resources.

**A small animal with a huge impact**
The first author of the publication in *Cell*, Dr. Alexandros K. Kanellopoulos, a postdoctoral fellow at DNF, is interested in the social behaviors associated with autism in the Drosophila, or vinegar fly. Drosophila is a wonderful model to study fundamental biological processes, and several scientific discoveries using this model system were so relevant as to receive the Nobel Prize. Still, it may seem surprising to use flies to also study human diseases, nearly 75% of human disease-causing genes are believed to have a functional homolog in the fly. This is why this small insect continues to be helpful in biology and medicine. For example, in addition to social interactions, this insect is used to study sleep, learning and memory because the respective molecular pathways are conserved in mammals, or more broadly in vertebrates.

**A closer look at the molecular mechanism**
Gamma-aminobutyric acid, commonly known as GABA, is a neurotransmitter, i.e., a chemical vector, that allows two neurons to communicate. The transmission of information between cells is important for the proper functioning of the brain. In their study, biologists used Drosophila with a mutation in a gene, *Cyfip*, which in humans (*CYFIP1*) has been associated to schizophrenia and autism. Mutant Drosophila show defects in several social interactions that

are, in humans, hallmarks of autism and other neurological disorders. The team demonstrated for the first time that GABA was trapped in the mitochondria of specific neurons called "GABAergic". "*We isolated the mitochondria and analyzed their GABA levels. We found that the GABA level was increased compared to that measured in Drosophila without the mutation and that this defect was caused by exaggerated mitochondrial activity*" explains Dr. Alexandros K. Kanellopoulos. Dysfunction of these small cellular structures thus causes problems with connections between neurons. This mechanism might contribute to socio-behavioural deficits observed in individuals with autistic disorders.
"*After examining hundreds of potential candidates and genetically testing 35, we have identified the molecule responsible for sequestering the neurotransmitter in the mitochondria. It is Aralar, a protein known to carry small molecules into the mitochondria. Here, we discovered that it also imports the neurotransmitter GABA*" describes Dr. Tilmann Achsel, co-author of the publication and researcher at the DNF.

**Preserved mechanism in mammals to new therapeutic prospects**
As part of their investigation, the researchers have modulated Aralar activity, resulting in an improvement in the social behaviour of the animals with the ASD- and SCZ-like mutation of the *Cyfip* gene. At the level of social interactions, the researchers followed well-established paradigms, not different from what we observe in humans, such as courtship, distance from each other (social distance), or competition for food. Pharmacologically treated fruit flies regain social competence.

Prof. Claudia Bagni and her colleagues have started to confirm their results in mice. "*We have concrete indications that this mechanism discovered in Drosophila is preserved in mammals*" adds Prof. Bagni. Indeed, the scientists have filed a patent with the PACTT office at UNIL and CHUV, which manages the intellectual property related to the invention. "*Based on our discovery and the impact it could have, we hope to raise the interest of the chemical and pharmaceutical industries to work together to develop new compounds directed to modulate Aralar*", says Prof. Bagni.

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