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A novel mechanism involved in attention-deficit hyperactivity disorder

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Researchers at the Angiocardioneurology Department of the Neuromed Scientific Institute for Research, Hospitalisation and Health Care of Pozzilli (Italy), have found, in animal models, that the absence of a certain enzyme causes a syndrome resembling the Attention Deficit Hyperactivity Disorder (ADHD). The study, published in the international journal *EMBO Molecular Medicine*, paves the way for a greater understanding of this childhood and adolescent disease, aiming at innovative therapeutic approaches.

Described for the first time in 1845, but came to the fore only in recent decades, ADHD is a disorder affecting children, generally diagnosed before age seven, with important effects persisting into adulthood. Its main features are frantic hyperactivity, serious difficulties in concentrating on activities, easiness to get distracted and marked impulsivity. Not to be simply confused with a "lively" childhood, it is a neuropsychiatric disorder causing difficulties with peers and, possibly, leading to learning problems. Yet, while currently available pharmacological treatments follow a symptomatic approach, little is known on the causes of the disease.

Now a group of researchers from the Neuromed Institute identified a molecular mechanism that, when dysregulated, causes the typical symptoms of children affected by ADHD. It is the PI3K gamma enzyme, involved in intracellular signaling. Already known for some time, this molecule has been studied primarily in the context of the cardiovascular and immune systems.

"We started right from those studies. - says lead researcher Daniela Carnevale - PI3K gamma has several interesting features, especially with regard to the functions which carries out in the heart and in the cardiovascular system. In this way, we already had animal models to study the enzyme in depth, particularly mice genetically lacking the enzyme, the so-called knock-out: these are very interesting models because, for example, they do not develop hypertension".

Animals lacking the enzyme, though, also behaved in a strange way. And it was this observation which led to a completely new line of research. "We had seen - continues Carnevale - that these mice had overly hectic movements, troubles in concentrating and learning, and they finally showed deficits in social interactions. In short, typical ADHD characteristics".

These observations led Neuromed researchers to focus their attention on the role that PI3K gamma could have in the nervous system, where the presence of the enzyme has recently been found. At the center of their study was a particular area of the brain, the Locus Ceruleus, already known because, through its connections with the cerebral cortex, it appears involved in maintaining attention. Dr. Carnevale and her collaborators showed that Locus Ceruleus hyperactivation leads to difficulties in maintaining attention and to hyperkinesis, features associated with learning deficits. "Locus Ceruleus neurons - she explains - have what has been defined a tonic discharge, a rhythm. In other words, they are a sort of pacemaker, and the regularity of their pulse has a crucial role in maintaining attention level. When these pulses are too frequent, as we have shown in mice lacking PI3K gamma, characteristic features of Attention Deficit Hyperactivity Disorder do appear".

The research offers a unique and completely new understanding of the mechanisms of this neuropsychiatric disease, so far only treatable with symptomatic drugs.

More information: "Lack of kinase-independent activity of PI3Kc in locus coeruleus induces ADHD symptoms through increased CREB signaling" EMBO Molecular Medicine (Online). DOI: 10.15252/emmm.201404697