Researchers analyze the effects of Ritalin on the developing brain

Tests with rats demonstrate that methylphenidate, non-commercial name of the medication, can affect a number of behavioral and neurochemical parameters, furthermore, leading to memory problems and neuron loss

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Methylphenidate is a central nervous system stimulant which is indicated for the treatment of ADHD and narcolepsy - Image: Christian Schnettelker/Flickr - CC by 2.0

Memory deficit, astrocytes and neuron losses, and decrease of ATP levels, the energy currency of the cells, are some of the effects the methylphenidate drug can have on the developing brain, according to the study conducted by researchers of the UFRGS Biochemistry Department on cell cultures and laboratory animals. The aim of the research, which was part of Felipe Schmitz's doctoral thesis, was to understand how the chronic treatment with the substance during childhood can affect behavioral and neurochemical parameters in the long-term.

Best known for its commercial name Ritalin, the methylphenidate is a central nervous system stimulant medication, indicated for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) and narcolepsy. In recent years, however, its indiscriminate use – either because of the inadequate diagnostic of ADHD, because of its use by people without the disorder, who seek to stay awake and focused in order to have a better performance when studying or at work, or even because of its use as a recreational drug – has raised concern among scientists and health professionals around the world. Despite its increasing consumption not only among children and teenagers, but also among adults (in Brazil, the rise was of 775% between 2003 and 2012, according to a study of Universidade do Estado do Rio de Janeiro), still little is known about its mechanism of action and long-term consequences.

"Although it has been used since the 1960's, the cellular mechanisms of this substance are still unknown. Because it has very similar effects to the amphetamines, researchers are concerned with the consequences, the effects of its long-term use, especially by young patients, such as children, the target audience to which the drug is usually prescribed," comments Felipe. "In the beginning, the medication used to be recommended for children who were a little older. But more recently, the drug has been administered earlier and earlier. After a child is born, it undergoes a long period of neurodevelopment, and this medication is being administered precisely during this period of development of the central nervous system," explains Angela Wyse, professor at the UFRGS Biochemistry Postgraduate Program, and counselor of the project.

Researchers also warn about the potential risk of wrong diagnostics of ADHD. Because there is no clinical marker for the disorder, diagnostics depend on a behavioral analysis, and, at times, the natural restlessness of the child can be misinterpreted as ADHD symptoms. "The Diagnostic and Statistical Manual of Mental Disorder establishes the criteria which should be taken into account to diagnose, or not, a child with ADHD. However, what we see in practice is that these criteria are often not being taken into account by practitioners in their day-to-day approach, at the medical laboratories," reports Felipe.

In order to mimic the situation of chronic use during childhood, the scientists injected methylphenidate in rats from their 15th to 45th day of life. This period would be equivalent to, in human terms, that of kids who would start to

take the drug in the beginning of their childhood – something between 4 and 7 years – and keep with the medication until the end of adolescence, or the beginning of adult life. Since the idea was not to analyze its efficacy on the treatment, but to investigate the effects which derive from its inappropriate use in children without attention deficit hyperactivity disorder, the scientists chose not to simulate the disorder on the rats.

It was observed that, in adult age, these animals presented alterations in some important aspects, including increase of inflammatory parameters, alterations in oxidative stress and in amino acids profile, and decrease on the ATP levels, molecule known as the energy currency of the cells, which is responsible for storing energy for their basic activities. Additionally, there was loss of astrocytes and neurons in the hippocampus, a cerebral structure which, besides being an important component of the limbic system (unit responsible for emotions and social behaviors), undertakes a fundamental role in the storage of short and long term memory and in the spatial memory (the one which allows you to locate yourself in space, to identify where an object is, or to find the way home).

The memory of the animals treated with the methylphenidate was affected as well. When compared to the control-group, they had worse performance on the spatial memory test (when put on an aquatic maze, they lost reference points and it took them longer to find the platform) and on the object recognition test (rats have an innate preference for novelty, therefore, they tend to spend less time exploring objects they remember to have seen before). Extreme cases of deficit in these types of memory are those of people with Alzheimer's, who lose the ability to recognize their loved ones, and forget where they are. "Biochemical alterations in the hippocampus and behavioral alterations which involve this cerebral structure are happening. And this cerebral structure is also very important for the formation of new neurons," states Angela.

The treatment with methylphenidate affected, on top of that, the dopaminergic system – areas of activity, paths and responses that involve the dopamine, a neurotransmitter which undertakes a series of important roles in the body, such as memory, and the sensation of pleasure and wellness. Tasty foods, sex, games and drugs are a few examples of situations which stimulate the action of dopamine. Its deregulation is related to neuropsychiatric disorders such as Parkinson's Disease and schizophrenia.

As the researcher explained, there is a fine balance between the various neurotransmitters in our brain, and any modification in this balance can result in damage to other structures. "The methylphenidate is an amphetamine, a psychoactive drug, it tampers with a neurotransmitter, with the dopamine. Cocaine also tampers with dopamine. Logically, cocaine has a much more devastating effect, but it destroys the dopaminergic neurons, and the individual gets addicted to it. That is why the drug can also be addictive, because it will release dopamine as well," Angela alerts.

The tests with cell cultures, in turn, were held in the United States of America, during Felipe's split site PhD at the University of New York, under the counseling of professor Moses V. Chao. The research was carried out with a group of cells called PC12, chosen because its structure is similar to the dopaminergic neurons structure. "We treated these cells with the methylphenidate and evaluated a series of proteins that are important to the memory and cell signaling, which regulates the death and survival of these cells. We observed that, indeed, a series of these proteins, of these extremely important elements, were affected by the treatment with methylphenidate in different ways," he explains. Among the main aspects observed there is an alteration in a protein called mTOR, which plays a relevant role in the production of new proteins. "When you involve memory, you also have protein synthesis. When we make new memories, we need to increase the protein synthesis. And we observed that a deficit of the mTOR happens, which is an important protein to start the process of protein synthesis. So, indirectly, it was observed that there seemed to be a decrease of protein synthesis. That is why we are also interested in observing whether this happens at a muscular level," Angela says.

The research findings show the complexity of the effects of a premature chronic exposure to the methylphenidate, and provide new basis to the comprehension of the neurochemical and behavioral consequences, and the mechanisms associated to the treatment with the psychoactive drug. It is important to emphasize, however, that the research did not entail analysis of the effectiveness of the medication, nor its effects on patints who have ADHD or any other illness. "We do not know what would have happened if that animal had been subjected to an attention deficit, if we would have had the same result we observed here," emphasizes the researcher. She also points out that methylphenidate is, currently, the best treatment for ADHD and narcolepsy symptoms. In such cases, therefore, the benefits would surpass the collateral effects. "A child who has attention deficit in fact needs to receive the medication. The problem is when the child does not have attention deficit and receives the medication," she reiterates, alerting for the importance of an interdisciplinary work for the ADHD diagnosis, and of testing other types of therapy before choosing the medicative treatment.

Upcoming projects

In their upcoming projects, the researchers intend to test the consequences of the intermittent methylphenidate intake in adult rats. The idea is to simulate sporadic consumption as a recreational drug, or the consumption by students who take the medication in tests season, for example. They also intend – based on research findings (theirs and others') which indicate that the drug intake compromises the protein synthesis, causes oxidative stress on the heart, and increases the overall risk of cardiac problems – to analyze the effects of the medication on the muscles and the heart.

Scientific article:

SCHMITZ, Felipe; CHAO, Moses V.; WYSE, Angela T.S. Methylphenidate alters Akt-mTOR signaling in rat pheochromocytoma cells. International Journal of Developmental Neuroscience, 2018.

Thesis

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Author: Felipe Schmitz

Counselor: Angela Wyse

Unit: Postgraduate Program in Biological Sciences: Biochemistry.

Translated by Laura Cristina Gay Reginin, under the supervision and translation revision of Elizamari R. Becker (P.h.D.) – IL/UFRGS.

Universidade Federal do Rio Grande do Sul
Av. Paulo Gama, 110 - Bairro Farroupilha - Porto Alegre - Rio Grande do Sul
CEP: 90040-060 - Fone: +55 51 33086000