Endocannabinoids and psychiatric disorders: *the road ahead*

Endocanabinoides e transtornos psiquiátricos: a estrada à frente

Nature – the leading science journal today – opened the New Year with an editorial entitled "A decade for psychiaty disorders". The Editor presented a bleak picture of recent advances in research and treatment. The hope that a single gene for schizophrenia or other mental illnesses will be found has evaporated into thin air. Most probably these diseases are based on many hundreds of genes that affect various aspects of brain development. Most of the drugs introduced over the last decades have not led to major disease improvement, but have mostly reduced the side effects of pharmacological treatments. Hence, the Editor concludes that "a deeper understanding of the underlying biology is essential to improve diagnosis and treatment".

Pharmacological treatments in psychiatry have depended too much and for too long on neurotransmitter systems and their agonists, such as dopamine, which has been known for over 60 years. I believe that the endocannabinoid system, more recently discovered and developed may shed new light on the physiological basis of psychiatric diseases and can be a breath of fresh air in psychiatric pharmacy.

Cannabis plant preparations have been used over millennia both as a medicine and as "a drug that takes away the mind" (as stated in ancient Assyrian clay tablets). Scientific-medical research on *cannabis* started about 150 years ago when a British colonial physician, W.B. O'Shaugnessy, and a French psychiatrist, J.J. Moreau, undertook clinical trials with Indian and North African *cannabis* respectively. The protocols of these trials would bring shudders to any modern regulatory committee, but their results are still of considerable interest. O'Shaughessy found that ethanol extracts (tincture) of *cannabis* resin, when administered to patients with rheumatism, tetanus, rabies, infantile convulsions, cholera, vomiting and *delirium tremens* gave positive results, which led to extensive use in the UK, where Indian *cannabis* resin was available. It was found to be useful in neurological diseases, but not in depression. Moreau, in one of the first publications published on experimental psychiatry, also recorded that *cannabis* was not an antidepressant, but in some 'cases of *delirium*' he had encouraging results. He described cases of 'temporary insanity' at the huge doses of *cannabis* administered. This parallels hypomania cases in South Africa, described more than a hundred years later, after use of *dagga*, which is known today to contain high concentrations of the active constituent, but no cannabidiol.

During the early part of the last century some progress was made on the chemistry and pharmacology of *cannabis*, but as the chemical picture was still unclear, interest waned. With the identification in 1964 of Δ^9-tetrahydrocannabinol (Δ^9-THC) as the active constituent of the plant, the cannabinoid field caught the interest of many research groups and hundreds of papers on the chemistry, biochemistry, metabolism, and clinical effects of this compound were published. However its mechanism of action remained unknown for nearly 2 decades. In the mid-1980's, the presence of a cannabinoid receptor in the brain was identified and shortly thereafter it was cloned. This was followed by the isolation of the major endogenous cannabinoids, anandamide and 2-arachidonoyl glycerol, the elucidation of their biosyntheses and degradations. This clarification of the chemical and biochemical background led to extensive research in a variety of biological and clinical fields. We are now in the midst of major advances in physiology and clinical applications, associated with the actions of the endocannabinoids.

Is the endocannabinoid system involved in psychiatric disorders? Most researchers in the fields will say that the answer is positive, but the experimental results are not straightforward. There are publications reporting enhancement of clinical symptoms by a specific cannabinoid and others reporting the opposite. Schizophrenia is one such disorder. In a recent report from Oslo, *cannabis* use was associated with better neurocognitive function in patients with a bipolar disorder, but the opposite was the case for schizophrenia subjects. Several groups have brought substantial evidence that *cannabis* abuse is a risk factor for psychosis in genetically predisposed people and may lead to a worse outcome of the disease and that the endogenous cannabinoid system itself is altered in schizophrenia (i.e., increased density of cannabinoid CB_1 receptor binding in corticolimbic regions and enhanced cerebrospinal fluid anandamide levels). Indeed a 'cannabinoid hypothesis of schizophrenia' has been suggested alongside the 'dopamine hypothesis'. However, in spite of the huge increase

in marijuana smokers over the past decades, the number of schizophrenic patients has not increased. It is possible that this surprising observation is due to the presence in *cannabis* of the nonpsychoactive cannabidiol, which has been found to be beneficial in the treatment of psychosis? There is also some evidence that specific genetic changes of the cannabinoid receptor 1 gene can act as a protective factor against schizophrenia.

The same picture is seen with anxiety. Users claim that *cannabis* smoking leads to lower anxiety and pharmacological stimulation of endocannabinoid signalling can produce anxiolytic behavioral responses. Low levels of endocannabinoids may result in anxiogenic behavioral responses in mice. But, anxiety reactions and panic attacks are the acute symptoms most frequently associated with *cannabis* use in humans. And again, as in psychosis, the nonpsychoactive cannabidiol, has been found – mostly from studies in Brazil - to be beneficial in the treatment of anxiety.

The simplest (but not necessarily correct) way to explain the above conflicting results is based on the well known biphasic effect of many cannabinoid actions. At low doses, cannabinoids may exert effects which are not seen at higher doses. Even opposing effects may be noted. As many cannabinoid effects are produced by affecting the levels of various neurotransmitters, one can assume that a cannabinoid may cause the release of a certain neurotransmitter at a low concentration, while at a higher concentration it may enhance the level of another one, leading to a different end result. Along the same line of speculation, the effect on the release of neurotransmitters may vary in different brain areas.

The positive effects of cannabidiol stem apparently from molecular mechanisms not associated with the cannabinoid receptors. Indeed, in many cases, its actions seem to be on the opposite side of those caused by THC – its neighbor in the *cannabis* plant.

A somewhat clearer picture appears in posttraumatic stress disorder (PTSD). A considerable amount of work, from various groups and in different countries, has shown that in animal studies CB_1 signaling is involved in the extinction of aversive memories. Indeed PTSD patients claim that *cannabis* use helps them considerably. Recently a Canadian study showed that nabilone (a THC-like drug) had beneficial effects on sleep in PTSD patients. On this basis, the Ministry of Health in Israel has approved medical use of marijuana for PTSD. As other human psychiatric disorders, such as phobia, appear to involve related pathological mechanisms, the endocannabinoid system might be a valuable therapeutic target for the treatment of these disorders.

Is the cannabinoid system also involved in emotional life and day-to-day mood changes? Is our psychological profile due, at least in part, to our endocannabinoid levels and brain area distribution? Are the interactions between the endocannabinoids and the neurotransmitters involved? Some highly original work points in this direction, but the full exploitation of this exciting area remains ahead of us.

I believe that the endocannabinoid system may shed light on the mechanism of some psychiatric diseases and possibly on some aspects of our psychological profile. I hope that further studies are carried out along these promising pathways.

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