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LETTER TO THE EDITOR

Would some cannabinoids ameliorate symptoms of autism?

Rami Bou Khalil

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Dear Sir,

There has been a massive growth of public awareness and research funding around autism spectrum disorders (ASD) over the past 10 years. This disorder is one of the groups of neurodevelopmental disorders known as pervasive developmental disorders characterized by three core deficits: impaired communication, impaired reciprocal social interaction and restricted, repetitive and stereotyped patterns of behaviors or interests. At present, there is no psychopharmacologic treatment for the core symptoms of autism.

In addition to their classic physiologic functions in diuresis, parturition and lactation, oxytocin and vasopressin act as important modulators of social cognition and behaviors in a diverse range of species including humans [1]. Some clinical studies have provided a body of evidence that raises optimism for the feasibility of oxytocin-based therapeutics in ASD. For example, administration of oxytocin to patients with ASD has been shown to facilitate processing of social information, improve emotional recognition, strengthen social interactions and increase eye gaze, and even reduce repetitive behaviors [2]. The effects of intranasal oxytocin on the social behavior of 13 patients suffering from high functioning ASD were investigated and compared to the effects of a placebo condition and to the behavior of matched healthy subjects. Oxytocin was shown to enhance visual scanning of faces and, in particular, of the eye region, as compared to a placebo condition. It enhanced patients' ability to process socially relevant cues and acquire their meaning in an interactive context such as the ball-tossing task [3]. The entangled evolutionary origins of oxytocin and vasopressin in mammals are noteworthy. Although oxytocin and vasopressin have profoundly different hormonal actions in the periphery, a rich body of evidence has shown that both neuropeptides can act on similar substrates in the central nervous system to regulate the related behaviors. These intertwined actions of oxytocin and vasopressin are realized pharmacologically through a phylogenetically related family of four G-protein coupled receptors that include an oxytocin receptor and the three vasopressin receptors (V1a, V2, and V1b). Only modest differences separate the affinity and potency of oxytocin for oxytocin receptor versus its nearest pharmacologic neighbor V1a [4].

Data suggest that the transient receptor potential V2 (TRPV2) protein may play a role in mediating physiological activities associated with oxytocin and vasopressin release, such as parturition, lactation and diuresis [5]. TRPV2 protein, also known as vanilloid receptor-like 1 (VRL-1), is a member of the TRP superfamily of nonselective, ligand-gated cation channels, many of which have been shown to serve as detectors and transducers of thermal sensory stimuli. It has been demonstrated that TRPV2 is activated by moderate thermal stimuli and, in the rat, is expressed in medium to large diameter dorsal root ganglion neurons [6].

Cannabidiol (CBD) is a major nonpsychotropic constituent of cannabis sativa, which unlike the other major constituent delta9-tetrahydrocannabinol (delta9-THC), is virtually inactive at both of its central nervous system receptors. In one study, cell-based calcium mobilization and electrophysiological assays were used to identify and characterize several novel cannabinoid TRPV2 agonists in

R. Bou Khalil (✉)
Psychiatric Hospital of the Cross, P.O Box 60096,
Jalledib, Lebanon
e-mail: ramiboukhalil@hotmail.com

R. Bou Khalil
Saint Joseph University, Beirut, Lebanon

cultured rat dorsal root ganglion neurons. Among these, CBD was found to be the most robust and potent, followed by delta9-THC and cannabinol [7]. Those cannabinoids may, accordingly, possess the ability, due to their action as TRPV2 agonists, to increase the release of both oxytocin and vasopressin enhancing the stimulation of oxytocin receptor and V1a receptors at the same time. CBD displays a plethora of other actions including anticonvulsive, sedative, hypnotic, antipsychotic, anti-inflammatory and neuroprotective properties. CBD and delta9-THC are components of drugs commercialized, in certain countries, as treatments for neuropathic pain, overactive bladder, and spasticity in patients suffering from multiple sclerosis [8]. Thus, despite their action on oxytocin and vasopressin release, CBD and delta9-THC may help in improving symptoms of ASD by their sedative, antipsychotic, anticonvulsant and tranquilizing effects. In addition, the cannabinoid system has already been shown to be implicated in social behavior in rats [9].

The administration of cannabinoids for children and adolescents suffering from ASD is a controversial legal and ethical issue. Instead, those cannabinoids may be tested when administered to animals presenting autistic symptoms. Animal models of autistic symptoms exist especially in rodents that have their oxytocin and/or vasopressin function impaired such as mice or rats lacking the oxytocin or vasopressin gene or one of their receptors [10]. Whenever cannabinoids were found efficient in animal models of autism, the rationale supporting their efficacy may outweigh their legal and ethical adversities, when administered to children in the setting of randomized controlled studies.

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