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REVIEW

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Biphasic effects of THC in memory and cognition

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Abstract

A generally undesired effect of cannabis smoking is a reversible disruption of short-term memory induced by delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis. However, this paradigm has been recently challenged by a group of scientists who have shown that THC is also able to improve neurological function in old animals when chronically administered at low concentrations. Moreover, recent studies demonstrated that THC paradoxically promotes hippocampal neurogenesis, prevents neurodegenerative processes occurring in animal models of Alzheimer's disease, protects from inflammation-induced cognitive damage and restores memory and cognitive function in old mice. With the aim to reconcile these seemingly contradictory facts, this work will show that such paradox can be explained within the framework of hormesis, defined as a biphasic dose-response.

KEYWORDS

Alzheimer's disease, biphasic dose response, cannabis, delta-9-tetrahydrocannabinol, hormesis, neuroprotection

1 | INTRODUCTION

Alzheimer's disease (AD) is characterized by progressive deterioration of cognitive functions and oxidative stress,[1] with biochemical alterations consisting in the accumulation of amyloid-β (Aβ) protein in the form of senile plaques[2] and intracellular neurofibrillary tangles (associated with hyperphosphorylated tau protein and neuronal cell depletion).[3-6] Although familial and sporadic AD differs in their cause, the progression of the disease from this point onwards appears to be the same. These alterations induce neuroinflammation and oxidative stress, which creates a neurotoxic environment that potentiates neurodegeneration and eventually leads to cognitive decline.[7,8] Also, Aβ-induced neurodegeneration elevates glutamate levels in the cerebral spinal fluid of patients with AD,[9] and cholinergic neurons are lost in brain areas relevant for memory processing (and accompanied by a decrease in acetylcholine).[10]

In normal conditions, memory, learning and behaviour depend on the proper function of the excitatory glutamate N-methyl-D-aspartate-receptor (NMDAR) and a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and underlying mechanisms of synaptic plasticity.[11-13] However, the dysregulation of intracellular Ca^{2+} homoeostasis[14] and excessive activation of the N-methyl D-aspartate (NMDA) subtype of the glutamate receptor, leading to excitotoxicity, are features of the AD brain.[15] All of the clinical mutations in the presenilin genes (PS1/PS2) that have been linked with the inherited form of AD disrupt calcium signalling,[14] which may contribute to subsequent neurodegeneration and memory impairments.[16]

2 | THC: FRIEND OR FOE OF THE HIPPOCAMPUS?

Analysis of the distribution of CB1 receptors shows that the hippocampus contains a high density of CB1 receptors,[17-21] and relatively large amounts of the endocannabinoids anandamide[22,23] and 2-AG.[23] Immunocytochemical studies have revealed that FAAH (fatty acid amide

hydrolase), the enzyme responsible for anandamide catabolism[24,25] and monoglyceride lipase, an enzyme that is believed to play a role in the hydrolysis of 2-AG[26,27] are significantly present within the hippocampus. Collectively, these findings demonstrate that the hippocampus is an important locus for cannabinoid effects on learning and memory.[28] The cellular and molecular mechanisms underlying THC's amnesic effect have been revealed in an elegant series of experiments by Puighermanal and colleagues.[29]

A generally undesired effect of cannabis smoking is a reversible disruption of short-term memory[30,31] induced by delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis. In addition, both acute and chronic exposure to cannabis are associated with dose-related cognitive impairments, most consistently in attention, working memory, verbal learning and memory functions in animals[32,33] and in humans.[34,35] In addition to reduced learning, heavy cannabis use is also associated with a decreased mental flexibility, increased perseveration and reduced ability to sustain attention.[36] Several lines of evidence suggest that the hippocampus, an area long implicated with learning processes, plays a major role in the mediating both the effects of exogenous cannabinoids on memory and endocannabinoid modulation of memory.[28]

Recent studies have, however, shown that THC paradoxically promotes hippocampal neurogenesis,[37,38] prevents neurodegenerative processes occurring in animal models of AD,[39-41] protects from inflammation-induced cognitive damage[42,43] and restores memory and cognitive function in old mice.[44,45] With the aim to reconcile these seemingly contradictory facts, this work will show that such paradox can be explained within the framework of hormesis, defined as a biphasic dose-response.

3 | HORMESIS HISTORICAL BACKGROUND

For several decades, it was believed that the dosage of a drug followed a linear pattern (at higher dose greater effect).[46] However, in subsequent years, many studies have shown an inverse response to different doses of a substance in the same individual, completely ruling out linearity and threshold response models.[47-49]

Hormesis is a dose-response phenomenon, characterized by a low-dose stimulation and a high-dose inhibition. The term hormesis was first introduced into the scientific literature in 1943 by Chester Southam and John Ehrlich,[50] mycology researchers at the University of Idaho, who reported that low concentrations of extracts from the red cedar tree enhanced the metabolism of a number of fungal species. The term hormesis was derived from the Greek meaning to excite. Prior to the report of Southam and Ehrlich,[50] there was a substantial history of reports in the biological literature also demonstrating a similar biphasic dose-response.

One of the first scientists to mention the biphasic effect was Paracelsus (1493-1541), who is recognized for his comments regarding the importance of the dose of chemicals in determining whether they are therapeutic or toxic.[51] He stated: "Alle Ding sind Gift, und nichts ohn Gift; allein die Dosis macht, daß ein Ding kein Gift ist," which can literally be translated as "All things are poison and nothing is without poison, only the dose allows something not to be poison." From this statement, the perception of the beneficial or harmful effects of chemical compounds has changed.[51]

After Paracelsus, other scientists have provided important data about this effect. As Tischner[52] points out, the opposite effects of the stimuli were already described by Hippocrates. The phenomenon is mentioned again in the eighteenth century, when the Austrian doctor, Gerard van Swieten (1700-1772) found that small doses of poppy juice cause the most animated sensations, while higher doses cause sleep and overdoses cause stroke.[53] In 1795, Hufeland writes in his treatise Ideen über Pathologie (Ideas on pathology) that the intensity of a stimulus makes a significant difference in the intentional response, that is, that the same stimulus can cause different effects if applied with degrees of intensity [cited in reference 54].

In 1854, Rudolf Virchow[55] reported that the movement of the bronchial epithelium cilia in the postmortem mucosa differed depending on the concentrations of sodium and potassium hydroxide. While at low concentrations cilia movement increased, a decrease in this movement was observed with high concentrations.[56] Three decades later, Hugo Schulz observed that the application of low doses of disinfectants increased the metabolism of yeasts, whereas in high doses, the metabolism decreased.[57] Although he initially dismissed the theory as the result of an experimental error, his repeated studies encouraged him to postulate the Arndt-Schulz law in association with Rudolf Arndt. This law states: "The physiological action of a cell is increased or decreased in relation to the intensity of the stimulus: small doses stimulate, moderate doses inhibit, and large doses kill".[57]

Another clear example of this biphasic effect is glutamate. This neurotransmitter plays a fundamental role in the functioning of the neural circuits involved in sensory processing, in learning, memory and in emotions. Low glutamate levels also activate adaptive stress responses that include the production of proteins that help to protect the neurons against more-severe stress. However, abnormally

high levels of glutamate at synapses can cause the degeneration and death of neurons.[58]

The hormetic effect is increasingly accepted, although there are some authors as Thayer et al,[59] who contended that little is known about the mechanisms underlying hormesis. Further, they argued that, in the absence of comprehensive mechanistic foundations, hormetic-like dose-response relationships are meaningless. It is incorrect to affirm that little is known about hormetic mechanisms. In fact, the case is just the opposite. As early as 2001, a series of articles was published on a range of endogenous agonists: prostaglandins,[60] nitric oxide,[61] estrogens and related compounds,[62] androgens,[63] adrenergic agonists,[64] adenosine,[65] serotonin,[66,67] dopamine[68] and opiates[69] that display hormetic biphasic dose-response. These articles documented that the mechanisms of biphasic dose-response were clearly established to the level of receptor and, in a number of cases, to further levels of molecular detail. Later assessments have identified dozens of hormetic mechanisms for immune responses[70] and for responses in tumour cell lines.[71] More recently, Calabrese[72] reported approximately 400 specific hormetic mechanisms across a broad range of biological models, endpoints and agents, with the quantitative features of the hormetic response being independent of mechanism.

4 | BIPHASIC EFFECTS OF THC AND ANANDAMIDE

The knowledge that cannabinoids display biphasic effects is not new; it was reported more than 40 years ago.[73] Contemporary reports include excitatory and depressant effects of THC on cortical evoked responses (over a dose range of about 0.5-3.5 mg/kg)[74] and on muscimol-induced circling behaviour (after intracerebral injections of Δ9-THC (1-10 μg),[75] and a biphasic anxiolytic/anxiogenic effect induced by 4 or 100 μg/kg, respectively, of the synthetic cannabinoid HU-210.[76] Other studies assessed the effects of the endogenous cannabimimetic anandamide over a wide dose range in a series of physiological and behavioural assays. These included the tetrad of tests in mice commonly used to evaluate cannabinoid-induced effects (motor activity, ring catalepsy, hypothermia and analgesia tests), as well as a model for agonistic behaviour. Results indicated that the higher doses tested (10-100 mg/kg) produced the well-known inhibitory effects in all of the above parameters. The lowest dose of anandamide tested (0.01 mg/kg) stimulated behavioural activities in the open field, on the ring and aggressive behaviour in timid singly housed mice. This dose of 0.01 mg/kg also stimulated phagocytosis, while higher doses (1.0 and 10.0 mg/kg) produced the opposite effects, namely inhibition of phagocytic activity.[77]

5 | BIPHASIC EFFECTS OF THC IN NEUROGENESIS

The hippocampal dentate gyrus in the adult mammalian brain contains neural stem/progenitor cells (NS/PCs) capable of generating new neurons, that is neurogenesis.[78,79] Chronic administration of the major drugs of abuse including opiates, alcohol, nicotine and cocaine has been reported to suppress hippocampal neurogenesis in adult rats.[80-83] However, pharmacological studies have demonstrated an important role for endocannabinoid signalling in promoting neuronal survival after cerebral ischaemia or trauma.[84] In addition, the important finding in 2004 of prominently decreased hippocampal neurogenesis in CB1-knockout mice (mice which lack CB1 receptors)[85] suggested that CB1 receptor activation by endogenous, plant-derived, or synthetic cannabinoids could promote hippocampal neurogenesis. One year later, Jiang et al[37] demonstrated that chronic treatment with both the synthetic cannabinoid HU210 and the endocannabinoid anandamide (AEA) promoted hippocampal neurogenesis and exerted anxiolytic- and antidepressant-like effects and made a reflective statement: "cannabinoids appear to be the only illicit drug whose capacity to produce increased hippocampal newborn neurons is positively correlated with its anxiolytic- and antidepressant-like effects".[37]

These findings are in contrast with those of Rueda et al,[86] who reported an inhibition of adult hippocampal neurogenesis. The differing regulatory effects of endocannabinoid shown in these studies may be produced by the opposing effects (hormesis) induced by high and low doses of exocannabinoids[87] and endocannabinoids.[77] In detailed examinations of the effects of HU210 on NS/PC proliferation, Jiang and co-workers[37] cultured embryonic NS/PCs (neural stem/progenitor cells) incubated with different concentrations of HU210 (synthetic agonist of THC). When 10 nmol/L to 1 μmol/L of HU210 were added to the culture medium containing the mitogenic growth factors bFGF and EGF, the WST-8 assay showed a significant increase in NS/PC proliferation, whereas 10 μmol/L produced profound toxic effects on cultured NS/PCs.[37] Rueda and co-workers[86] used a 5 μmol/L AEA concentration and detected an inhibition of neuronal differentiation. Based on these reports, it is evident that at low concentrations (up to 1 μmol/L), cannabinoids are able to induce neurogenesis, while at higher concentrations, neurogenesis is impaired.

6 | THC PARADOX IN MEMORY

The majority of research undoubtedly demonstrates that THC in high concentrations impairs memory and cognition, due to their ability to inhibit cholinergic transmission in the

limbic system and cortex, and the memory deficits observed with THC resemble those seen following administration of cholinergic antagonists.[88]

Unfortunately, scientists have looked only at one side of the coin due to the inability or refusal to see beyond the current models of thinking.[89] A paradigm is a set of assumptions, concepts, values and practices that constitute ways of viewing reality for the community that shares them, especially in an intellectual discipline.[89] The next example illustrates how paradigms have negatively influenced scientific research. The first major effort to explore whether drugs could enhance learning in animal models was undertaken at the University of California at Berkeley in the Department of Psychology during the 1960s. While these efforts extended earlier preliminary investigations at the University of Chicago and elsewhere, the Berkeley group created a new research direction that lead to the development of valuable drugs in the treatment of cognitive disabilities as seen with Alzheimer's disease (AD) and related diseases of ageing. In fact, the initial breakthrough was undertaken by then two graduate students (James McGaugh and Lewis Petrinovitch), who hypothesized that memory was related to the concentrations of acetylcholine released by the neurons. With this guiding framework, these students tried to determine why some mice were bright (ie smart), and others were dull (ie not so smart). To test this hypothesis, they administered a drug over a broad dose range to the bright and dull mice that would prevent the normal breakdown (ie hydrolysis) of the acetylcholine. The agent used to slowdown the normal breakdown of acetylcholine was physostigmine, a natural constituent of the Calabar bean. The treatment was expected to make the dull mice brighter and the bright mice even brighter, but only up to a point, that is, when the dose exceeded a hypothetical optimal zone, triggering a decline in performance. Both dull and bright exhibited the characteristic U-shaped dose-response relationship, thereby confirming the study hypothesis. The manuscript based on these findings was rejected by the editor because "the results of your paper upset a fundamental pharmacological assumption that no drug improves behaviour." One of the two students persevered, publishing a paper several years later,[90] opening up a new era in the psychology and pharmacology of learning and memory research.[91]

It has long been recognized that an important element of the action of THC may be its ability to inhibit cholinergic transmission in the limbic system and cortex.[88] Early studies revealed that Δ9-THC reduced uptake of choline in the hippocampus, thereby restricting acetylcholine synthesis.[92,93] Several cannabinoid agonists have been shown to inhibit electrically evoked acetylcholine release in hippocampal slices[92,94] and synaptosomes.[95] Similarly, microdialysis studies in awake rats also showed cannabinoid-induced decreases in acetylcholine release.[96,97] This effect on hippocampal acetylcholine release is clearly CB1 receptor-mediated, as all the afore-mentioned studies demonstrated that SR-141716 (a CB1 receptor antagonist) blocks the effect.[28]

The dominant paradigm affirming that THC impairs memory and cognition has been lately challenged by a group of scientists who has shown that THC is also able to improve neurological function in old animals when chronically administered at low doses. Such improvement could be related with THC's capacity to inhibit AChE (acetylcholinesterase, the enzyme that catalyzes the breakdown of acetylcholine), thus increasing ACh levels, as well as preventing AChE-induced Aβ aggregation by binding in the peripheral anionic site of AChE, the critical region involved in amyloidogenesis. It is noteworthy that THC is a considerably more effective inhibitor of AChE-induced Aβ deposition than the approved drugs for Alzheimer's disease treatment, donepezil and tacrine, which reduced Aβ aggregation by only 22% and 7%, respectively.[98]

7 | DOSE- AND AGE-DEPENDENT EFFECTS OF THC ON MEMORY

Compelling data have shown that memory is also affected in a biphasic fashion. Puighermanal and colleagues[29] studied mice treated with vehicle or different doses of THC (0.3, 1, 3 and 10 mg/kg, i.p.) immediately after the training session in the object recognition test. Doses of 3 or 10 mg/kg induced a significant amnesic-like effect tested 24 hour later, while lower doses did not produce memory deficits. A similar result was reported by Han et al[99] who used a 5 mg/kg dose of THC, and Varvel et al[88] who observed memory deficits with 10 mg/kg of THC. These results clearly demonstrate that memory impairment is due to the use of high THC concentrations. Conversely, other scientists showed that THC at an extremely low concentration (2.5 nmol/L), and other synthetic agonists at similar concentrations have the capacity to slow or halt Alzheimer's disease progression by reducing the synthesis of its major pathological marker, amyloid beta.[39,40,100]

In addition to this positive effect at low concentrations, there is evidence that Cannabidiol (CBD) is able to block some negative effects of THC.[101,102] The hypothesis that cannabidiol impacts on the effect of Δ9-THC was firstly postulated by Rottanburg et al,[103] who found an increased prevalence of psychotic disorders among users of cannabis with high Δ9-THC content and lack of cannabidiol, and was confirmed by other researchers, who found that cannabis with high-CBD content is associated with fewer psychotic experiences than cannabis with low-CBD content.[104,105] It has also been observed that cannabidiol, co-administered with 9-THC, significantly reduced the

psychotomimetic symptoms induced by Δ9-THC,[106] and that pretreatment with CBD prevented the acute induction of psychotic symptoms by delta-9-tetrahydrocannabinol.[107] Additional studies have provided evidence that wild-type mice chronically receiving THC + CBD do not exhibit memory impairment.[41] This observation supports previous work showing that CBD is able to antagonize THC-induced deficits in memory tasks[108-110] and highlights the relevance of combining the two natural cannabinoids, THC and CBD, to mitigate the negative consequences of THC administration.[101] These findings show that the combination of THC and CBD exhibits a better therapeutic profile than each cannabis component alone and supports the consideration of a cannabis-based medicine as potential therapy against Alzheimer's disease.[41] A novel research found that CBD attenuates a spatial working memory impairment caused by THC in monkeys.[110] The potential of CBD to ameliorate cognitive effects of THC shows that studies in monkeys may be more translational than those in rodents; these results also suggest that a requirement for CBD-high marijuana cultivation may be a potential regulatory avenue for harm reduction in the face of increased liberalization of recreational and medical marijuana laws.[110]

Moreover, a contemporary investigation[44] showed that a chronic low dose of Δ 9-tetrahydrocannabinol (THC) restores cognitive function (reduction of memory deficits and increased learning capacity) in old mice. This behavioural effect was accompanied by enhanced expression of synaptic marker proteins and increased hippocampal spine density. The authors showed that THC exposure in mature and old mice (12 and 18 months, respectively) restored cognitive function to a level similar to that in young untreated mice. By contrast, they found in young adult mice (2 months old) that THC exposure has a deleterious effect on cognition, a finding that is in agreement with previous studies[33,41,111,112]

The beneficial effects of low-dose THC administration are dependent on an epigenetic mechanism involving histone acetylation.[44] This is in line with previous findings showing that enhanced histone acetylation can result in recovery of cognitive abilities in old mice.[113] Attempts to reverse age-related epigenetic processes through a pharmacological blockade of histone deacetylases have shown some promise in rodents,[114,115] but the deleterious side effects have prevented application in humans.[116] Consequently, the generalized inhibition of histone deacetylation is not further considered to be a suitable treatment of age-related pathologies. In contrast, cannabis preparations and THC are used for medicinal purposes. They have an excellent safety record and do not produce adverse side effects when administered at a low dose to older individuals. Thus, chronic, low-dose treatment with THC or cannabis extracts could be a potential strategy to slow down or even to reverse cognitive decline in the elderly.[44] Furthermore, a recent study[45] demonstrated that a single injection of an ultra-low dose of THC (0.002 mg/kg) can reverse age-dependent cognitive decline in female mice. However, it should be emphasized that the ameliorating effect of ultra-low THC on cognitive performance of naïve mice was restricted to old animals, while in young animals (2-3 months old mice), the same treatment induced a minor, though significant, long-lasting cognitive deficits.[111,112] The endogenous cannabinoid system is known to have a dual, age-dependent role in the regulation of memory and learning.[117] In agreement with this fact, recent evidence shows that a repeated low dose of THC improves cognitive performance in a mouse model of neurodegenerative disease in old mice, whereas it induces memory impairment in healthy mice.[41]

In a comprehensive review, Sarne and colleagues[118] discussed these opposite effects of ultra-low doses of THC in terms of "conditioning" where a minor insult activated an endogenous compensatory system that protected the organism from other insults. Thus, it was not surprising to find that, ultra-low THC improved memory in naive old mice, which were cognitively impaired due to ageing, similarly to its effect in challenged young mice which were cognitively impaired due to neurotoxic insults.

Recently, Calabrese[119,120] provided the first extensive documentation and assessment of the dose-response features of pre- and postconditioning studies that conform to an hormetic dose-response. The range and diversity of preconditioning agents are extensive, involving a complex array of pharmacological, chemical and mechanistic approaches. Furthermore, Calabrese[120] provided the first report that hormetic dose-response occur for both early and delayed preconditioning-induced protection.

In addition to biphasic dose-response, there are mechanisms that are known to contribute to the dual effects of cannabinoids, such as age and stage of development of the organism, acute vs. chronic application; immediate vs. delayed response or the dependency of the effect on the physiological status of the organism.[42-45,121-123]

8 | CONCLUSIONS

The biphasic dose-response model challenges long-standing beliefs about the nature of the dose-response in a low dose zone. Many researchers did not focus on the low dose stimulatory responses provided in their tables and figures, choosing to address only the high concentration effects.[124] Paradigms affect the way scientists do research: they serve to define what should be studied, what questions should be asked, and what rules should be followed in interpreting the answers obtained.[125]

For many years, most scientists dogmatically accepted that THC impairs memory. This paradigm was supported by teachers, researchers, scientific papers and academic institutions. In his book: the structure of scientific revolutions, Thomas Khun[89] wrote that "scientific revolutions are those noncumulative developmental episodes in which an older paradigm is replaced in whole or in part by an incompatible new one. A scientific revolution occurs, according to Kuhn, when scientists encounter anomalies that cannot be explained by the universally accepted paradigm within which scientific progress has thereto been made. Such anomalies are the base for the construction of a new paradigm:

THC modulates memory and cognition in a biphasic and age-dependent manner: in old animals, low concentrations improve memory and cognition while high concentrations impair these functions; in young animals, even a low concentration is detrimental.

These findings coincide with what has been observed in humans: an irrefutable evidence that the use of marijuana affects the memory and cognition mainly in young people. This is very important because the idea that marijuana is a "soft" drug and that it is not dangerous has been generalizing. We argue that healthy young people should not smoke marijuana or ingest cannabinoids. The beneficial effects of low THC concentrations seem to apply only to old people with neurological impairment due to ageing or some neurodegenerative disorders like Alzheimer.

From the pharmacological standpoint, it has been suggested that studies evaluating the effects of neurotransmitters, hormones or virtually any other substance should involve a wider concentration range with the aim to detect their full spectrum of effects.[58]

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