The cannabis paradox: when age matters

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New evidence in mouse models reveal that exposure to delta9-tetrahydrocannabinol (THC), the main psychoactive component in *Cannabis sativa*, may improve cognitive performance in aging animals.

Time changes everything, and our brain is not an exception. As we age, our cognitive abilities may deteriorate undoubtedly affecting everyday life activities. But, what if we could prevent such cognitive decline in the elderly? One of the components of cannabis, THC, may have in fact a solution. While there is still an ardent debate on the advantages and drawbacks of cannabis, cannabis derivatives are the most consumed illicit substances worldwide. Cannabis users are estimated to be 7.5-10% of the population aged 12 or older in United States[1] and Europe[2]. Phytocannabinoids, contained in cannabis, by supplanting the endogenous cannabinoids (endocannabinoids) modulate the endogenous cannabinoid system. This is a neuromodulatory system composed by receptors, endocannabinoids and the enzymes involved in their synthesis and degradation, that regulates a range of physiological functions, including learning, and memory [3]. The main cannabinoid receptor in the brain is CB1 receptor, responsible for most central effects of THC[4]. In this issue, Bilkei-Gorzo et al.[5] reveal the divergent effects of a long-term exposure to a relatively low dose of psychoactive cannabinoid THC[6], on cognitive performance in mice of different ages (Figure 1). They attribute these effects to signaling through CB1.

The authors first show that THC exposure in mature and old mice (12 and 18 months old mice, respectively) restored cognitive function to a level similar to that in young untreated mice. In contrast, they found in the young adult mouse (2 months old) that THC exposure has a deleterious effect on cognition, in agreement with other studies using a variety of learning and memory tests[7].

The authors then investigated the mechanisms involved in the paradoxical effects of THC focusing on the hippocampus, a brain region intimately linked to cognitive performance. They found that the synaptic density in this brain region, inferred from the expression of synaptic proteins in the hippocampus, dropped in aged mice compared to young mice but that levels were restored to that of young mice, after chronic THC treatment. Furthermore, they found that the gene expression profile of the hippocampus of the THC-treated mature mice resembled vehicle-treated young mice, while the profile of THC-treated young mice was similar to vehicle-treated mature mice. Among the many genes differentially expressed, the authors pinpointed klotho, transthyretin and brain-derived neurotrophic factor (BDNF) as being up-regulated in THC-treated mature mice, compared to untreated mice, all of them linked to life span, cognitive modulation and synaptic plasticity. In contrast, the two most strongly down-regulated genes observed in THC-treated mature mice - connective tissue growth factor and caspase 1- regulate pro-ageing processes. Thus, the authors' data suggest that these genes are good candidates to sustain the observed cognitive improvement in THC-treated mature animals.

The authors were then able to identify a potential mechanism that might mediate the effects of improved cognition by THC treatment in aging mice. In these mice, they identify enhanced phosphorylation of hippocampal signaling pathways relevant for learning and memory such as cAMP response element-binding protein (CREB) and extracellular-signal regulated kinase (ERK), compared to untreated mice. In addition, these older treated mice had enhanced histone acetylation in the hippocampus, an epigenetic modification linked to active gene transcription. This enhanced acetylation was found in the klotho and BDNF promoters in THC-treated mature mice. Further proof for a role for this histone acetylation in the effects of THC treatment on synaptic

density in aged mice came from the concomitant administration of an acetyl transferase inhibitor during THC exposure. Using this combination on aged mice resulted in no change in cognitive ability, expression of synaptic markers, acetylation of histones, or change in the expression of klotho and BDNF compared with untreated aged mice. Importantly, mature mice lacking the CB1 receptor in the main forebrain glutamatergic neurons did not show any of the benefits of the THC treatment in those parameters studied.

The present study supports a valuable and unexpected effect of THC in the elderly, as compared to young adults, but also opens the debate on a number of issues. First, the study raises the question of the translational relevance of the discoveries in mice. At what age, and under which circumstances would an individual be susceptible to obtain the described beneficial effects of THC? Trying to make a parallelism with humans, in a clinical setting the study would involve 3-4 years of sustained THC treatment. It should be taken into consideration that during ageing several deleterious processes such as neuroinflammation, oxidative stress, mitochondrial disarray and degradation of aberrant molecules impairment converge in the brain[8], triggering a loss of neural plasticity and function, which in the absence of proper cell turnover can lead to cognitive decline. Thus, as in the mice, in humans THC could specifically target those degenerative events occurring in the ageing brain leading to a different response in young and healthy individuals. In agreement with this idea, recent evidence shows that a repeated low dose of THC improves cognitive performance in a mouse model of neurodegenerative disease, whereas it induces memory impairment in healthy mice[9], while direct klotho expression enhancement improves cognitive performance in a mouse model of Alzheimer's[10], all potentially related to the mechanism described by Zimmer's team[5].

The second question raised by this study has to do with the drug used. THC activates CB1 receptors, but also other not so abundant cannabinoid receptors. According to the present study, the use of more selective drugs than the phytocannabinoid THC should show similar effects as those described by Bilkei-Gorzo *et al*.[5] Conversely, and in relation with this second question, would *Cannabis sativa* preparations be as beneficial as THC? THC is one of at least 85 cannabinoids present in cannabis preparations. Such a complex blend of cannabinoids with diverse activities over the organism (some complementary, but others antagonistic or even independent from those of THC) combined with their varied relative abundance in the diverse cannabis plant strains and preparations, are rarely well controlled. Therefore, such considerations will have to be addressed in future studies in order to understand whether cannabis preparations are suitable, and will be necessary to obtain medical-grade products that could benefit from the mechanisms described by Bilkei-Gorzo *et al*.[5].

Considering the increase in human lifespan world wide, the promotion of healthy ageing is currently a priority, as well as, an economic and social challenge. The study by Bilkei-Gorzo *et al*. [5] opens the door to a potentially novel approach in preventing the cognitive consequences of ageing by using THC. Only complementary clinical studies will reveal whether we may benefit from those effects found in ageing mice.

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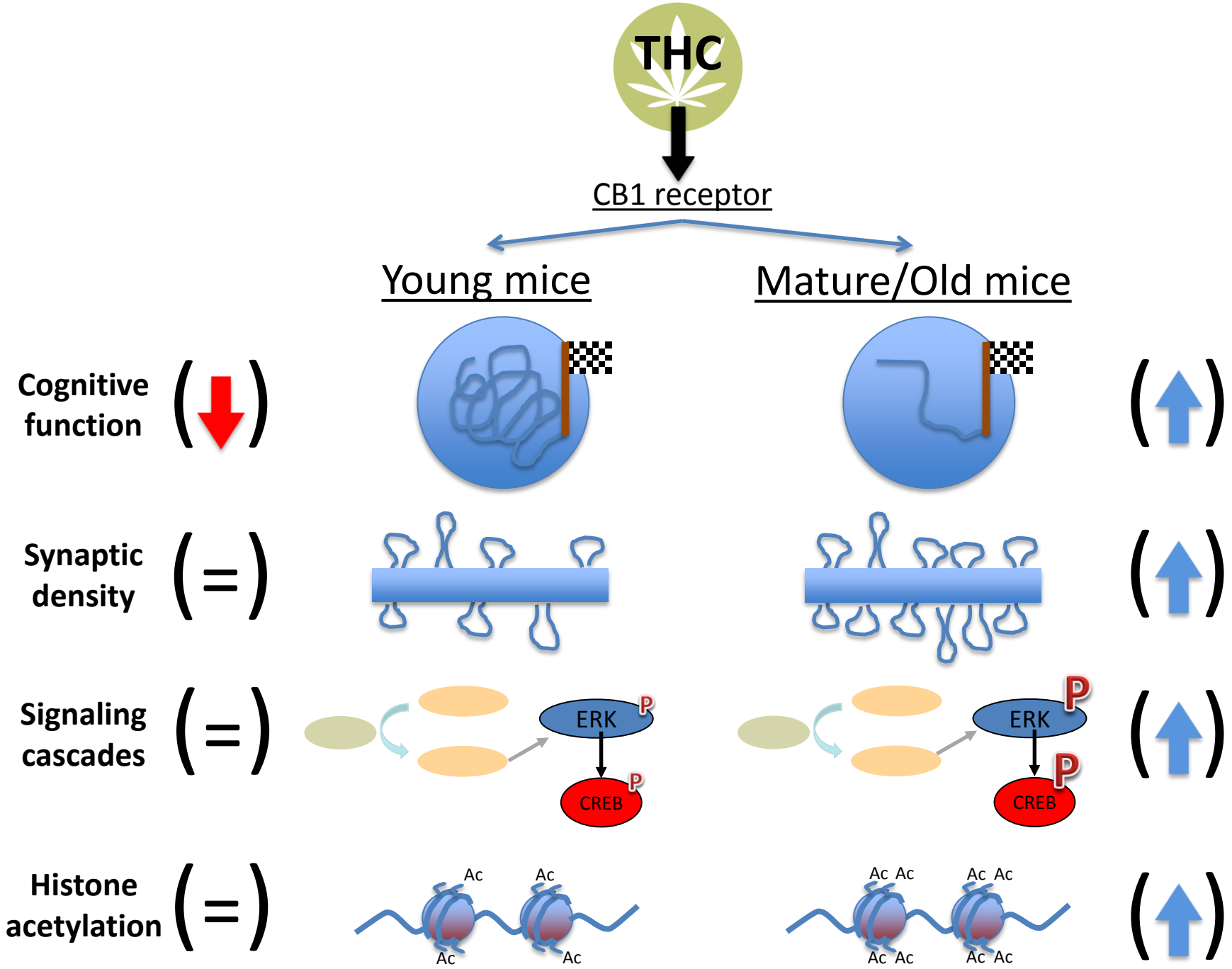
Figure legend

Figure 1. Bilkei-Gorzo *et al*. now show that delta9-tetrahydrocannabinol (THC) improves, through a CB1 receptor mechanism, cognitive performance, the density of hippocampal synapses, the phosphorylation of signaling pathways involved in learning and memory, and histone acetylation in the hippocampus of mature/old mice. Instead, in the young mice, THC has no such effects or its effects are detrimental.



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