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The effects of Δ9-tetrahydrocannabinol on the dopamine system

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Preface

Δ^9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis, is a pressing concern to global mental health. Patterns of use are changing drastically due to legalisation, availability of synthetic analogues ('*spice*'), cannavaping and aggrandizements in the purported therapeutic effects of cannabis. Many of THC's reinforcing effects are mediated by the dopamine system. Due to complex cannabinoid-dopamine interactions there is conflicting evidence from human and animal research fields. Acute THC causes increased dopamine release and neuron activity, whilst long-term use is associated with blunting of the dopamine system. Future research must examine the long-term and developmental dopaminergic effects of the drug.

Introduction

Cannabis is a widely used recreational drug. Over half of young Americans have used the drug1. In Europe cannabis has now overtaken heroin as the most widely reported illegal drug used amongst people entering specialist addiction services2. At the same time, political

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debates about changes to the legal status of the drug continue internationally. Although causality has not been conclusively demonstrated, heavy cannabis use is associated with increased risk of mental disorder3 including psychosis4, addiction5, depression6, suicidality7, cognitive impairment8 and amotivation9.

Δ^9-Tetrahydrocannabinol (THC), cannabis' main psychoactive component10, elicits its acute psychoactive effects via the endocannabinoid type 1 (CB_1) receptor (CB_1R)11. THC has been linked to the rewarding aspects of cannabis and the induction of symptoms of mental illnesses and cognitive impairment. Lately the THC content of cannabis has been increasing12, synthetic THC analogues (potent cannabinoid agonists; termed *'spice'*) are now widely used13. The future consumption of cannabinoids through electronic cigarettes ('*cannavaping*') and edible products14 changes the landscape further15. Given the widespread use of cannabinoids, and the links between THC exposure and adverse outcomes, it is imperative to understand the neurobiological effects of THC. Recently, we and others have found that heavy cannabis use is associated with reductions in dopaminergic function. Since the rewarding and psychotogenic effects of THC and its analogues are thought to be mediated by the dopaminergic system, demonstrating dopaminergic alterations *in vivo* in human users is of clinical relevance for the prevention and treatment of cannabis use disorders and psychoses. Therefore, we review the animal and human literature on the complex effects of acute and longer-term THC on dopamine synthesis, release, and its receptors, critically analysing the factors that contribute to effects, and variations between studies, before finally providing a framework for future research including pharmacologically dissecting these effects, especially in the developing brain.

THC receptor binding in the brain

THC is a CB_1R and endocannabinoid type 2 receptor (CB_2R) partial agonist11. The psychoactive effects of THC are blocked by the CB_1R antagonist rimonabant16,17 indicating that these are mediated through activating G-protein-coupled CB_1R receptors which reduce cyclic adenosine monophosphate (cAMP) levels by inhibiting adenylate cyclase18. THC disrupts finely-tuned endocannabinoid retrograde signalling systems due to the temporal and neuronal specificity of endocannabinoids over THC. Under conditions of low CB_1R density, THC antagonises endogenous agonists possessing greater receptor efficacy than THC19. THC also allosterically modulates opioid receptors20, which may provide additional indirect routes for altering dopamine transmission21. Furthermore, THC has psychoactive metabolites with CB_1R affinity, further complicating the analyses of receptor binding studies22.

CB_1 receptors and dopamine

Early animal studies described the interactions of amphetamine, which increases dopamine release, and THC23. These reported that amphetamine's behavioural effects were potentiated or antagonised depending on the dose of THC leading researchers24 to propose that dopamine was *"a prime candidate for…the mode of action of Δ^9-tetrahydrocannabinol".* Indeed, THC produces complex effects on the dopamine system, contributing to the drug's recreational and harmful effects. However, there are inconsistencies between the preclinical and clinical findings which challenge the field. It is thus timely to review the evidence and

provide a framework for understanding the inconsistencies between the preclinical and clinical findings.

Dopaminergic neurons are modulated by the endocannabinoid system (eCBS)25. CB_1Rs and the endocannabinoid ligands anandamide and 2-arachidonoylglycerol (2-AG) are abundant in dopaminergic pathways including the striatum26 where they act as a retrograde feedback system on presynaptic glutamatergic and γ-aminobutyric acid (GABA) nerve terminals (Fig. 1) to modulate dopamine transmission. Anandamide27 and 2-AG28 stimulate dopamine release in the nucleus accumbens (NAc) shell. This effect is blocked by the CB_1 antagonist rimonabant, indicating that dopaminergic effects of endocannabinoids involve CB_1 receptors. The rewarding properties of THC via increased dopamine release and dopaminergic neuron firing are underpinned by biased signal transduction mechanisms from the CB_1R16. There is evidence of differential effects of acute *vs.* chronic THC exposure on the dopaminergic system. Therefore, we will treat these separately and describe the effects on different neurobiological components of the dopaminergic system including neuron firing, synthesis, release, reuptake and receptors.

Acute THC and presynaptic dopamine in animals

From the outset it was clear that THC exerts complex effects on the dopamine system. Early *in vitro* studies in rodents using radiolabelled dopamine in synaptosomes found that THC caused increased dopamine synthesis31 and release24 (Fig. 2). However, the effects on dopamine uptake yielded conflicting results, with evidence of both increases32 and dose-dependent decreases24. Subsequently biphasic and triphasic effects of THC were discovered, whereby low doses of THC produced increases in the conversion of tyrosine to dopamine, but high doses of THC resulted in decreased dopamine synthesis33. Likewise, complicated temporal relationships between THC administration and changes in dopamine levels were observed34, such that repeated dosing results in behavioural and neurochemical tolerance –highly pertinent to the mechanisms of dependence to the drug. The complex dose-specific effects of THC in rodents were thought to be due to dose-related decreases in precursor uptake32 and dopamine-opioid interactions via μ-opioid receptors31.

Subsequent work investigated THC-induced increases in dopamine synthesis *in vivo*. THC increased [^{3}H]-dopamine synthesis35,36, tyrosine hydroxylase37 and messenger ribonucleic acid (mRNA) expression38, the rate-limiting step in the dopamine synthesis pathway. Similarly, increases in dopamine metabolism, measured with the dihydroxphenylacetic acid/dopamine (DOPAC/DA) ratio, were reported in most39 but not all37 rodent studies. However, the majority of early studies using spectrophotofluorimetry were inconsistent due to technical limitations in detecting the rapid changes in extracellular dopamine concentration detectable by microdialysis techniques used more recently40.

In vivo microdialysis shows that acute THC increases dopamine efflux in the prefrontal cortex (PFC)41, striatum42 and nucleus accumbens (NAc)43. Only one study did not find THC–induced increases in dopamine efflux44, which may have been related to route of administration since that study used a THC gavage whereas the other studies used intravenous injection which produces a rapid increase in THC which reaches the brain

promptly compared to gavage which favours sequestration in lipid compartments due to the very high lipid solubility of THC45. Differences in microdialysis results are associated with the strain of experimental rat46. Electrophysiological studies in rats have categorically demonstrated that THC dose-dependently increases firing rates in ascending midbrain dopaminergic projections via CB_1R agonism47,48. Taken together, these findings suggest THC increases the firing rates of dopamine neurons which leads to increased dopamine synthesis and release in terminal fields.

Acute THC and post-synaptic dopamine in animals

Acute THC did not alter dopamine receptor proteins levels in rhesus monkeys49. In the rat limbic forebrain, one study reported increased dopamine type 1 receptor (D_1R) availability50 whilst other studies reported decreases51. In the striatum, dopamine type 2 receptor (D_2R) density showed either a decrease51 or no significant changes, whilst decreases in D_1R have been reported50. Taken together, the findings of no change in receptor protein levels together with a tendency for reduced receptor availability most likely reflects THC-induced changes in synaptic dopamine levels. .

Acute THC and dopamine in humans

Studies of metabolic brain activity in humans using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) provide indirect measures of dopaminergic function through changes in cerebral blood flow and glucose metabolism. These serve as surrogate markers of brain activity in areas with dopaminergic projections. In humans, acute THC is associated with increased activity in frontal and sub-cortical regions52. However, as the CB_1R has the highest concentrations in these regions53 these findings may be due to direct endocannabinoid effects rather than reflecting dopamine-mediated processes. When studies of acute THC on resting brain activity have focussed on regions with dense dopaminergic innervation, such as the striatum, there have been inconsistent effects, with reports of both increased and reduced activity52. However, certain cognitive tasks are modulated by dopaminergic signalling and may provide a more robust proxy for THC-induced changes in dopaminergic transmission. For example, motor response inhibition is associated with cortical dopamine release and an fMRI study in healthy humans with previous exposure to cannabis found that THC attenuates activation in the right inferior frontal cortex and the anterior cingulate cortex (ACC) during suppression of motor inhibition54. Further indirect evidence of blunted dopaminergic processing comes from a study in healthy humans with previous exposure to cannabis using a verbal working memory task whereby THC attenuated striatal activation55 and a study of reward function in occasional cannabis users, which found that THC induced a widespread attenuation of the brain response to feedback in reward trials56 but not under reward anticipation conditions56.

It is also possible to directly measure the dopamine system using molecular imaging. These studies have examined the effect of acute THC on dopamine in humans with previous exposure to cannabis *in vivo*. Using PET, a combined analysis57 of two previous studies has shown that THC does indeed cause dopamine release in the ventral striatum in the human brain57. Likewise, acute THC challenge elicited dopamine release in fronto-temporal cortical brain regions58, although this finding requires replication with radiotracers that

show higher affinity for cortical dopamine receptors. However, in a separate study using single photon emission computed tomography (SPECT) no significant THC-induced dopamine release was observed,59 which may be due to a relatively small sample size (n=9). This is because THC-induced dopamine release in the striatum appears to be of a lower magnitude than that caused by other drugs such as amphetamine and methylphenidate60, combined with difficulties in imaging dopamine changes that are comparatively small61.

Repeated THC and pre-synaptic dopamine

Studies of repeated THC dosing have yielded complex, regionally-specific effects including increased total striatal dopamine levels62 in rats but reduced hippocampal63 dopamine levels in mice. Reduced dopamine metabolism was found in the medial PFC in two rat studies62, an effect which was not observed in the striatum or the NAc64. THC administration for 21 days down-regulated tyrosine hydroxylase mRNA expression in the substantia nigra and ventral tegmental area (VTA) midbrain nuclei, but not in the cortex or striatum65. In the NAc, several studies have reported that multiple THC doses do not significantly change dopamine release66 in rats. However, this may be due to differential dopaminergic responses within the NAc, as in one rat study repeated THC doses led to increased dopamine release in the NAc core but decreased release in the NAc shell67. The picture is further complicated by genetic strain effects whereby increased dopamine release in the NAc was observed in Lewis but not Fischer 344 rat strains68. Taken together, these studies indicate that repeated THC dosing produces regionally-specific effects on dopamine function.

Human studies in cannabis users

Several molecular imaging studies of dopaminergic function have been conducted in human cannabis users. Using PET, dopamine synthesis capacity was reduced in cannabis users69. Importantly, this reduction was driven by users meeting clinical criteria for abuse or dependence and was related to the severity of cannabis use (Fig. 3). Likewise, in two separate studies, cannabis users displayed reduced dopamine release to a stimulant challenge which was inversely related to severity of cannabis use70 and cognitive deficits including poor working memory71. Since no alteration in amphetamine-induced dopamine release was seen in recently abstinent cannabis users72, this effect is likely related to active use of the drug. While chronic use was not associated with altered stress-induced dopamine release73, there was evidence of a positive relationship between duration of cannabis use and stress-induced dopamine release in the limbic striatum73. Likewise, there is recent data showing that cannabis users have an attenuated metabolic response to methylphenidate challenge in the striatum, with a negative relationship between methylphenidate-induced metabolic increases and severity of cannabis use74. There is also evidence of reduced dopamine transporter (DAT) density in chronic cannabis users75. Whilst the interpretation of some of these studies is complicated by cannabis users also smoking tobacco, a recent experiment has addressed this by studying cannabis users without comorbid substance dependence, to show that cannabis users do indeed have reduced dopamine release71. Overall there is converging evidence for reduced presynaptic dopaminergic function in cannabis users.

Repeated THC and post-synaptic dopamine

Studies in rats have reported that multiple THC dosing results in increased D_2R availability in the midbrain, striatum and PFC65,77 and that this is associated with dopamine receptor sensitisation. There is further evidence of downstream dopaminergic effects of THC, as one study in rats78 reported up-regulated postsynaptic dopamine receptor signalling in the NAc via increased adenylyl cyclase activity, which was proposed to underlie THC-induced changes in amphetamine-induced locomotive behaviour. These findings suggest that repeated THC dosing results in altered dopamine receptor signal transduction.

Dose-dependent increases in burst firing in the VTA in response to multiple THC administrations have been reported in nearly all murine electrophysiological studies48, with one exception79. In the substantia nigra pars compacta (SNpc), multiple THC dosing was associated with increased firing, although this was smaller in magnitude than in the VTA80,81. This suggests that VTA and SNpc dopamine neurons develop a differential response to repeated THC exposures. There also appears to be an effect of withdrawal from multiple THC doses whereby decreased firing is elicited by abrupt cessation of repeated THC or administration of the CB_1R antagonist SR141716A82.

Recent human studies in current and abstinent ex-cannabis users have found no significant difference in striatal D_2R availability compared to individuals with no history of chronic cannabis use70–72,83–85. However, there was an inverse relationship between age of first cannabis use and D_2R availability in one study72 and an inverse relationship with current cannabis use in another study83, suggestive of possible dose-effects or susceptibility to drug use.

THC exposure and dopamine cell morphology

In addition to changes in function, there is evidence from studies in rodents that THC exposure causes abnormalities in the structure of dopamine neurons. These morphological effects are region-specific and include reductions across a range of measures of neuronal cell size in the VTA86,87 and increased neuronal arborisation in the NAc shell and frontal cortex88.

Developmental THC exposure and dopamine

Adolescence is an important time for brain development and adolescent cannabinoid exposure has consequences in adulthood89. The eCBS plays an important role in brain development90 and developmental THC exposure produces complex alterations in the dopamine system which are apparent from an early stage. For example, gestational THC exposure is associated with increased foetal brain tyrosine hydroxylase mRNA expression in rats91 and changes in dopamine receptor gene expression. THC exposure in early development was associated with increased cortical D_2R availability92. In rats, exposure from gestational day 5 to post-natal day 21 resulted in decreased NAc D_2R gene (*DRD2*) mRNA. Likewise, human maternal cannabis use was associated with decreased foetal NAc *DRD2* mRNA93. Early life exposure to THC also blunts the dopaminergic response to stimuli that release dopamine later in life, such as stress and amphetamine. This was seen in

the hypothalamus, striatum and limbic forebrain94, and frontal cortex95. In a study of CB_1R agonist self-administration in rats96, THC exposure during adolescence enhanced the reinforcing effects of cannabinoids in adulthood, suggesting that exposure to THC during adolescence increased addiction potential during a critical period of development. Importantly, THC-exposed rodents had a reduced capacity for cannabinoid induced increases in firing of dopaminergic neurons, consistent with a blunting of the dopamine response in adulthood.

Inconsistencies between animal and human work

Preclinical evidence shows that acute THC increases in nerve firing rates and animal studies using microdialysis indicate that acute THC challenge causes dopamine release, yet the results of experiments from human studies have not been consistent97,98. There are a number of factors, which may underlie the inconsistencies in the results of the studies presented above.

The animal evidence indicates that there are highly region-specific differences in dopamine activity following THC administration including differential dopaminergic responses in the shell and core of the NAc67. However, whilst human PET imaging provides a reliable measure of dopaminergic function in the striatum61, the spatial resolution of most PET cameras is approximately 4 mm which limits its accuracy for measuring activity in small brain volumes (such as the core and shell of the NAc) due to partial volume and spillover effects99. For the foreseeable future, therefore, human *in vivo* imaging techniques lack the spatial resolution to detect these complex effects on different parts of the dopamine pathway and research on living complex human brain tissue *in vitro* raises significant ethical challenges100.

A further possibility underlying the lack of consistent dopamine release in the human studies is that the dose of THC used in human imaging studies has not been sufficient to consistently elicit measurable dopamine release. Human studies all administered 10mg or less of THC because older pharmacological studies indicated that the “standard joint” (defined by the US National Institute on Drug Abuse) delivered an approximate THC dose of 8mg-15mg, equivalent to about 170 micrograms/kg101. These doses are significantly less than those used in animal microdialysis studies, which are typically around 1 mg/kg. Likewise, the THC content of cannabis has increased significantly since early clinical studies102, such that THC doses may be over 40mg per *spliff* (joint; cannabis cigarette)103, so the doses that were used in the published imaging studies no longer reflects typical THC exposure in cannabis users. The picture is further complicated by animal data which indicate that THC exerts complex dose-dependent effects on the dopamine system33 and the dose-response profile for THC-induced dopamine release has not been investigated in humans so it remains possible that human imaging is missing peak dopamine changes. Likewise, heterogeneity in the animal data may be a reflection of time of sampling in relation to THC treatment. For example, repeated daily THC administration led to an initial decrease in dopamine levels followed by a gradual return to baseline in brains that were studied one hour after THC dosing, but increases were subsequently observed two hours post-dose34. This time period is consistent with acute release and diffusion away, followed by up-

regulation of synthesis to increase levels at 2 hours. Alternatively, factors that may contribute to the complex temporal course of dopaminergic effects include intricate changes in dopamine synthesis and metabolism. These comprise CB_1R-mediated increases in tyrosine hydroxylase activity38 along with acute increases and longer-term decreases in monoamine-oxidase activity104, such that THC may exert differential effects on the time courses of dopamine synthesis and degradation. Equally, the partial agonist properties of THC on the CB_1R only serve to obfuscate its dopaminergic effects since THC can both activate and block cannabinoid receptors, in a regionally specific and species-dependent manner based on the density and efficiency of populations of receptors and the concentrations of endogenous agonists19.

There are a number of challenges in assessing the long-term effects of exposure to THC. Firstly, it is plausible that discrepant findings may be attributable to the duration of THC treatment. Animal experiments are typically conducted following administration of THC for no longer than three weeks65,81,87 whilst human studies are conducted in participants who have taken cannabis over years (the duration of regular cannabis use is typically 3+ years76). Furthermore, it remains unclear to what degree homeostatic mechanisms are able to compensate for these alterations over time. Additionally, in humans there are a number of psychosocial and genetic risk factors that may predispose an individual to develop a cannabis use disorder. Given animal evidence of interactions between early life psychological deprivation and THC-induced effects on dopamine77, it is possible that the human data in cannabis-dependent participants is confounded by a range of environmental factors including parental loss, amongst other psychosocial factors105. Other environmental and physiological factors have been found to influence the dopaminergic effects of THC. Of particular potential human significance is sleep deprivation, which decreases dopamine turnover in response to THC106; and stress, which increases THC-induced dopamine synthesis107. Likewise, cannabis contains a multitude of other compounds, called phytocannabinoids, which likely exert differential and complex actions on the dopamine system which could have resulted in the varied response in human cannabis users *vs.* the more consistent animal data using THC only. Similarly, due to co-morbidity of addictions, it is particularly challenging for human imaging researchers to recruit participants with cannabis dependence who do not use other psychoactive compounds, including nicotine and alcohol, in more naturalistic studies.

Finally, whether THC is delivered in a contingent or non-contingent way is likely to be important given evidence that anticipation leads to dopamine release. In general, the animal studies include a variety of contingencies around the dosing of THC. In contrast, in the human acute studies THC was given to participants with a prior exposure to the drug but was not delivered in the habitual manner in which the drug is consumed, which may have reduced the degree of dopamine release.

Dopamine and the behavioural effects of THC

THC is associated with a number of behavioural effects which likely involve alterations in dopaminergic function. The first evidence of this came from early animal studies, which reported similarities between the behavioural effects of THC, including catalepsy and

hypothermia108, and dopamine antagonists109. Likewise, THC antagonises the locomotor and hyperthermic effects of amphetamine, which causes dopamine release110. These seemingly paradoxical effects may be due to the high doses used in the early research together with the partial agonist effects of THC and/or non-specific receptor-independent effects.

THC promotes increased food intake in animals111 and humans112, colloquially referred to amongst users as “the munchies”. Since appetite is modulated by the dopamine system113, studies have investigated dopaminergic involvement in THC-induced feeding, finding that the dopamine D_1 receptor antagonist SCH23390 attenuated THC-induced feeding at a dose that did not affect feeding on its own114. Recent research has identified CB_1R mediated changes in hypothalamic pro-opiomelanocortin (POMC) neurons115 as potentially underlying this process via mitochondrial uncoupling protein 2 (UCP2), which is involved in ghrelin-mediated dopaminergic function116.

Heavy cannabis use is associated with impaired educational and occupational outcomes117. Factors that may underlie this include cognitive impairment, including involving executive dysfunction118, working memory impairments119 and amotivation120, defined as reduced motivation for goal-directed behaviour121. These functions are susceptible to mesocortical dopaminergic manipulation122 including prefrontal D_1 receptor blockade123, for example. Whilst a preclinical study reported that D_2 receptor antagonism blocks THC-induced working memory deficits124, this was not replicated in humans125. Nonetheless, there is recent evidence that THC-induced working memory deficits are moderated by catechol-*O*-methyltransferase (COMT), a key enzyme in the dopamine metabolic pathway126, which also modulates the effects of THC in adolescence on dopaminergic cells size87. Heavy chronic cannabis use produces apathetic behaviours in rhesus monkeys127 and a study in humans76 found that reduced dopamine synthesis capacity observed in heavy cannabis users was inversely related to amotivation. An overlapping feature of the amotivational syndrome associated with cannabis use disorders is negative emotionality128, such as reduced reward sensitivity and negative emotionality was also found to be inversely related to methylphenidate-induced dopamine ventral striatal dopamine release70.

The dopamine system is involved in risk for psychosis129. An early case report described increased striatal dopamine following cannabis intoxication associated with the exacerbation of psychotic symptoms in a patient with schizophrenia130. Furthermore, cannabis users with a diagnosis of schizophrenia and those at clinical high risk for schizophrenia displayed blunted striatal stress-induced dopamine release131. Although dopamine release was blunted in cannabis users with schizophrenia, it was nevertheless directly related to the induction of psychotic symptoms132. Supersensivity of post-synaptic D_2 receptors65 could explain this apparent paradox, or it could be due to impaired endocannabinoid regulation of dopamine signal transduction. Supporting the latter explanation, patients with schizophrenia using high levels of cannabis show reduced anandamide levels133, and cannabidiol, a compound that elevates anandamide levels, has been shown to reduce psychotic symptoms134. Alternative post-synaptic mechanisms include CB_1R-D_2R heterodimerisation135 and downstream intracellular mechanisms including the neuregulin 1-

erb-b2 receptor tyrosine kinase-phosphoinositide 3 kinase-protein kinase B (*NRG1-ERBB4-PI3K-AKT1*) pathway136.

Outlook

There is now a substantial body of evidence in animals showing that THC exerts effects on the dopamine system. The key challenges for the field must be to understand the complexity of these effects, how these translate to humans and relate to the potential negative effects of the drug in humans (Box 2). Animal studies demonstrate that acute administration of THC causes region-specific increases in dopamine release and nerve activity and we must understand the functional significance of this. The available preclinical evidence suggests that chronic THC administration causes long-term changes on the dopamine system, but a general limitation of these models is that they do not reflect typical patterns of human use. Thus future studies should be of longer duration to reflect human use. This should also include co-administration with other drugs such as nicotine and alcohol that are commonly used with cannabis. Related to this is a need to understand how the dopaminergic effects of THC are moderated by the other phytocannabinoids. Human PET studies have demonstrated blunted dopamine synthesis and dopamine release in cannabis users relative to non-users, yet we still need to understand the precise mechanisms through which this occurs.

A key outstanding question remains “are the effects of THC on the dopamine system reversible, and, if not, at which point do these changes become irreversible?” Likewise, further molecular imaging studies in humans are needed to determine the dose-response and timing of the acute effects of THC on dopamine release, and to determine if there are regional differences in dopamine release, particularly between cortical and sub-cortical regions.

Ultimately, a key challenge in interpreting the animal and clinical work is the use of different techniques, some of which cannot be conducted in humans. Likewise, we must reach consensus on THC dose equivalence across species. It is therefore difficult to know what the implications of some preclinical work are for human research and how to back-translate human findings into preclinical models. We must move out of silos and use translational techniques, such as PET and MR imaging approaches that can be conducted in humans and preclinical models that capture human use patterns in combination with traditional preclinical techniques. We must also understand how the psychoactive metabolites of THC, and the endocannabinoids modulate THC-induced changes in dopaminergic function.

Given changing patterns in cannabis use across the world, particularly in young people, and the consumption of cannabis with higher THC content, there is clearly a pressing need to understand how THC alters dopaminergic function. This is especially important given the emerging evidence that dopaminergic alterations are linked to a number of the adverse cognitive and behavioural consequences of THC, and the lack of current effective biological interventions for many of the psychiatric sequelae of cannabis use. Dopaminergic dysfunction may thus represent an area for future treatment targets.

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The evidence that gestational exposure to THC is associated with dysregulated dopamine synthesis in later life has major potential public health implications given the prevalence of cannabis use in women of child-bearing age and that the liberalisation of cannabis laws around the world may be associated with increased use of the drug amongst gravid and nursing mothers. However, questions about the developmental effects of THC remain. In particular, how long do the dopaminergic effects persist and what are their behavioural consequences? A related critical question is what are the effects of THC exposure during adolescence on the dopamine system?

In summary, the available evidence indicates that THC exposure produces complex, diverse and potentially long-term effects on the dopamine system including increased nerve firing and dopamine release in response to acute THC and dopaminergic blunting associated with long-term use. Future research should focus on probing the relationships between cannabis-induced alterations in the dopamine system and behavioural effects in humans and animal models.

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Box 1: Glossary of methods used to assess dopaminergic activity after THC exposure

- High performance liquid chromatography (HPLC): A technique to separate, identify and quantify a particular chemical from a mixture.
- In vivo electrophysiology: A method of studying single neuron responses by using microelectrodes to record from cells, including in the living animal brain.
- Microdialysis: A technique used for continuous measurement of neurochemicals and metabolites by inserting a probe into a specific area of brain.
- Positron Emission Tomography (PET): An imaging technique that uses a positron-emitting radiotracer that binds to specific proteins including receptors, enzymes and transporters. The gamma rays produced by the radionuclide allow quantification of proteins in living tissue non-invasively with very high chemical specificity.
- Single photon emission (computed) tomography (SPECT): An imaging technique similar to positron emission tomography, but with lower spatial resolution.
- Synaptosome: A homogenized mixture of isolated synaptic terminals.

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Box 2: Strategy for future work.

Preclinical and Clinical Research

- Determine the relationships between cannabis-induced alterations in the dopamine system and behavioural phenomena in humans and animal models.
- Use translational techniques that can be applied in human and animal studies alike and employ study designs that better reflect patterns of human use, including modelling contingency in acute THC challenge studies
- Consensus needed on dose equivalence across species.
- Determine if THC-induced dopaminergic changes during key developmental phases persists into later life and if this is linked to behavioural changes
- Investigate how gene variants that modulate the endocannabinoid and dopamine systems influence the sensitivity to the rewarding effects of THC and the vulnerability to addiction, amotivation and psychosis following chronic exposures
- Investigate the effects of sex in THC response. This will be useful to understand the different susceptibility to cannabis effects that have been reported between males and females74.

Preclinical Research

- Determine the effects of long-term THC exposures on the dopamine system alongside co-administration with nicotine to reflect typical patterns of human use.
- Determine the mechanisms underlying the complex dose-response effects of THC on dopaminergic function.
- Elucidate the mechanisms for regional differences in dopaminergic effects and the functional significance of this on behaviour.
- Determine if the long-term effects of THC are reversible with abstinence.

Clinical Research

- Determine if the blunted dopamine release and synthesis seen in chronic users is a pre-existing vulnerability factor or a direct result of repeated THC exposure.
- Determine the dopaminergic changes over the course of repeated THC exposures and dose-response effects.
- Consensus needed in the human literature on how to report previous exposure to cannabis use.
- Determine if there are regional differences in dopamine release to THC in humans.

- Determine the dose and the context dependency for THC effects on the dopamine system.

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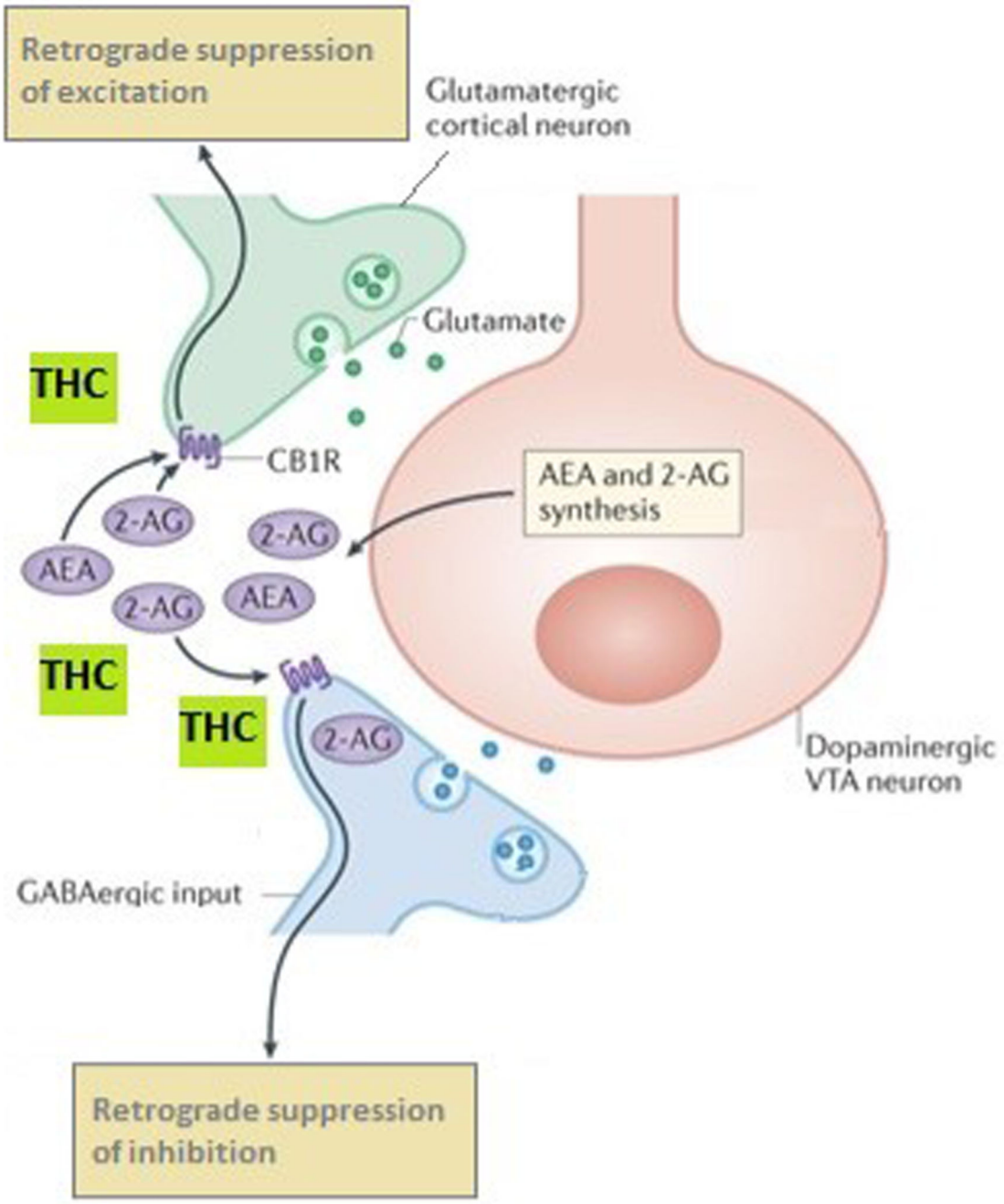

Fig. 1. THC binds to CB1 receptors on glutamatergic and GABAergic neurons disrupting normal endocannabinoid retrograde signalling from dopaminergic neurons137.

Endocannabinoids (eCBs) influence ventral tegmental area (VTA) synaptic signalling. 2-Arachidonoylglycerol (2-AG) is synthesised by diacylglycerol lipase (DAGL) in dopaminergic VTA neurons and, once released, retroactively acts on endocannabinoid type 1 receptors (CB_1Rs) on nearby glutamatergic and γ-aminobutyric acid (GABA)-ergic terminals. CB_1Rs mediate robust inhibition of GABA inputs onto VTA dopamine cells29, termed retrograde suppression of inhibition. CB_1Rs are also localized on glutamatergic terminals synapsing on VTA dopamine neurons30 where eCBs mediate retrograde

suppression of excitation. Thus, eCBs fine-tune the activity of the mesolimbic dopamine projections through modulating both excitatory and inhibitory signalling. THC disrupts this finely tuned system.

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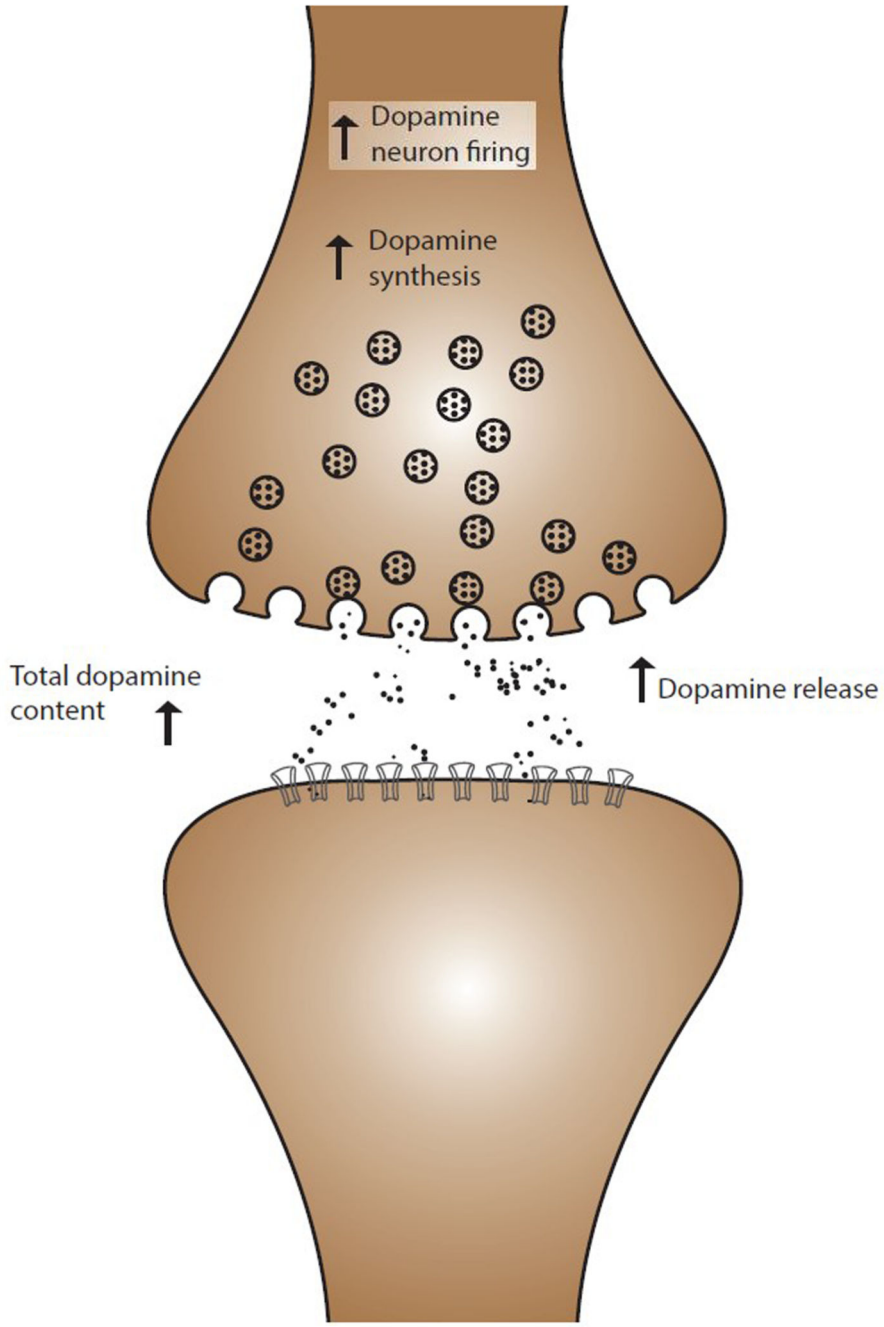

Fig. 2. Summary of the acute effects of THC on dopaminergic function.

In animal models acute THC challenge is associated with increased dopaminergic cell firing, increased dopamine synthesis and increased dopamine release.

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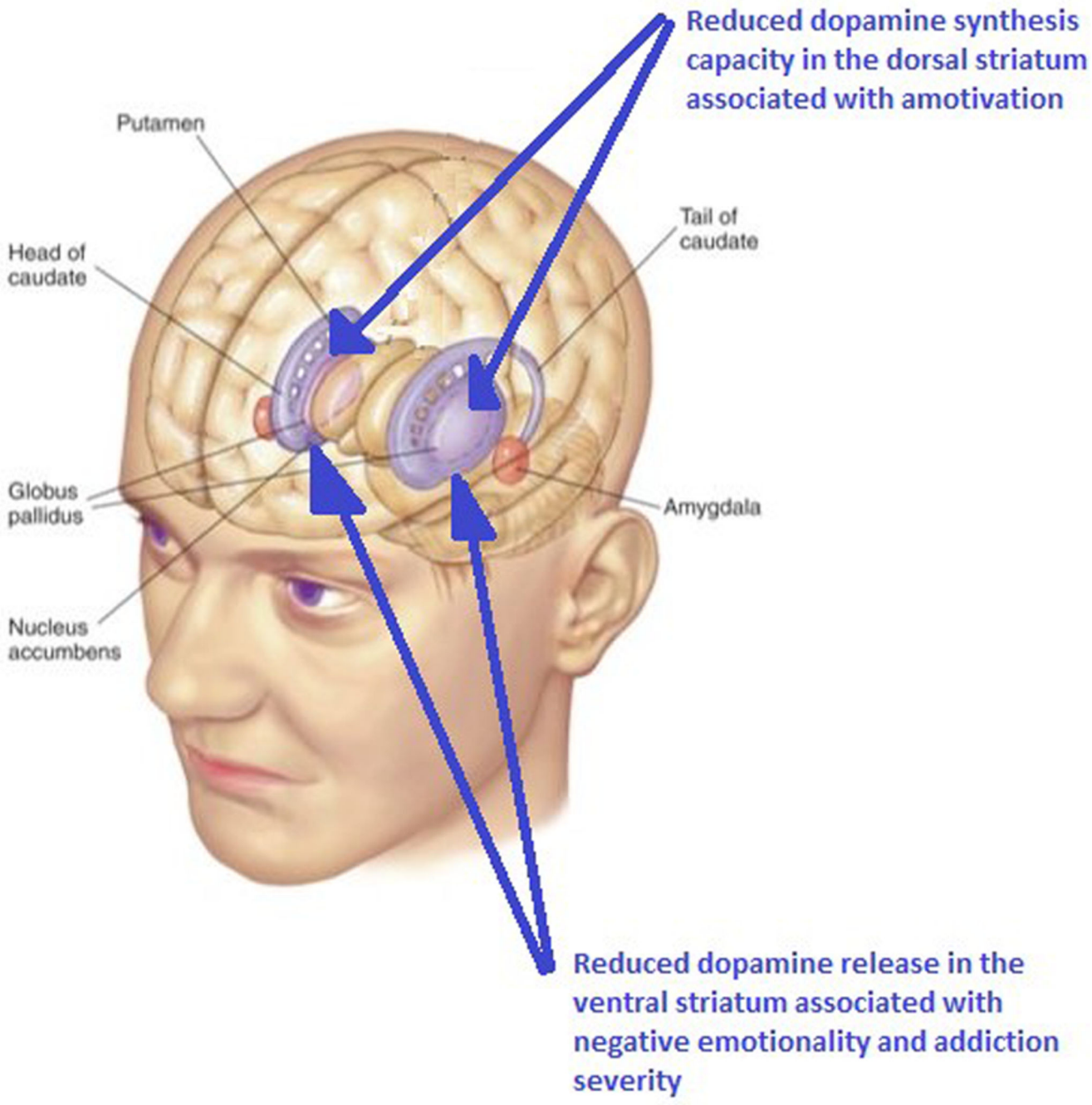

Fig. 3. Cannabis use in humans is associated with reduced dopamine in the striatum. PET studies have shown lower striatal dopamine synthesis and release capacity in cannabis users.

Lower dopamine synthesis capacity in the dorsal striatum is directly associated with reduced motivational levels76 and reduced dopamine release in the ventral striatum is directly associated with negative emotion levels and addiction severity70