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Using dopamine research to generate rational cannabinoid drug policy

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Abstract

The recent rise in the recreational use of synthetic cannabinoids (e.g. 'K2' and 'Spice') has been accompanied by a corresponding increase in regulation. Besides prohibition of specific compounds and general class bans in over forty states, five synthetic cannabinoids (CB) are federally regulated under a 'temporary' ban and are currently under a formal review to determine whether to permanently schedule them. Whether through explicit prohibition of specific chemicals, or potential *de facto* bans of unofficially scheduled compounds through the analogue act, scheduling CBs may significantly impede researching their therapeutic utility and elucidating physiological roles of the endogenous CB system. We argue that a review of neuroscience research suggests that synthetic CBs that act like Δ^9-tetrahydrocannabinol (THC) by directly binding to and stimulating CB receptors (i.e. direct agonists), as well as novel drugs that indirectly stimulate these receptors by increasing levels of endogenous CB neurotransmitters (i.e. indirect agonists) have therapeutic value. Specifically, neurochemical research into how CBs influence mesolimbic dopamine release, a reliable and consistent marker of drugs' rewarding/reinforcing effects, provides the most useful indication of CB abuse liability, and may have implications for the generation of rational drug policy. It demonstrates that direct CB receptor agonists, but not indirect agonists, increase mesolimbic dopamine release. Thus, while direct CB receptor agonists pose an abuse liability, indirect agonists do not. We recommend regulatory agencies revise policies that treat these separate CB classes similarly and to curb regulation aimed at any CB receptor agonists as Schedule I, as this ignores their medicinal properties.

Keywords

Drug Policy; Drug Schedule; Endocannabinoids; synthetic cannabinoids; cannabinoids; voltammetry

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Introduction

Rise in synthetic cannabinoid use is accompanied by regulation

Between 2009 and 2011, the number of annual calls to poison-control centres associated with the recreational use of synthetic cannabinoids (e.g. ‘K2’ and ‘Spice’) rose from 14 to roughly 7000,[1] a shift that has been accompanied by a corresponding increase in regulation.[2] Close to half of US states have enacted general class bans or prohibition of all cannabinoid agonists,[3] while the majority of remaining US states have banned exhaustive lists of cannabinoids. Five of these drugs (JWH-018, JWH-073, JWH-200, CP-47,497 and its C8 homologue) exist in Schedule I through federal ‘temporary’ bans,[2,4] which can effectively enact a *de facto* prohibition of other unregulated cannabinoid receptor agonists due to the analogue act.[5] Since these compounds were regulated through ‘emergency’ mechanisms, initial review of the therapeutic properties and biological effects of these drugs may not have been as carefully considered. A thorough examination of scientific research into the compounds’ addictive properties and therapeutic properties is essential to avoid excessive regulation.

While some synthetic cannabinoids (CBs) pose risk for abuse (i.e. direct CB receptor agonists), there is considerable variation among these chemicals in the degree to which they possess a liability for recreational use or the development of compulsive patterns of drug consumption. Here we argue that examination of neurochemical, neuropharmacological, and behavioural research suggests that some classes of CBs exhibit no rewarding/reinforcing effects and high therapeutic value (i.e. indirect CB receptor agonists). Therefore, any policy that bans all cannabinoid agonists, either explicitly or in a *de facto* manner, will impede their medicinal usage, the development of therapeutics, and much-needed research to further elucidate the endogenous cannabinoid system.

Measurements of cannabinoid-induced dopamine release provide a strong measure of abuse liability

When studying the addictive properties of a compound in the laboratory, investigators must determine which measures will most accurately reflect the abuse liability of a drug. Neuroscience research into the addictive potential of CBs has demonstrated the difficultly of establishing behavioural animal models to accurately assess their rewarding/reinforcing qualities;[6,7] as a result, we suggest that neurochemical markers are considered when enacting policy because they provide consistent and robust indications of CB abuse potential.[8,9] The behavioural measures frequently used for this purpose, such as self-administration,[7] conditioned place preference,[7,10] and intra-cranial self-stimulation,[11] have historically provided weak and inconsistent results. As previously discussed,[6,7] CBs may be less suited for the typical battery of behavioural tests for abuse liability because their unique pharmacokinetic profile (slowonset and long half-life), their tendency to produce catalepsy and sedation, and their ability to produce anxiogenic (anxiety-producing) and aversive effects at high doses reduce their capacity to function as strong reinforcers. However, measurements of dopamine release in the mesolimbic system, a pathway implicated in reward,[11] provide a reliable metric to evaluate the rewarding/reinforcing qualities of CBs from a neuroscientific perspective.

All drugs of abuse increase dopamine levels in the nucleus accumbens (a terminal region of the mesolimbic dopamine system originating from dopamine neurons in the ventral tegmental area of the midbrain and projecting to the forebrain), an effect which is thought to significantly contribute to their reinforcing and rewarding qualities.[11] Although the precise role mesolimbic dopamine plays in reward processing remains contentious,[11,12] there is little doubt that it contributes significantly to drug reinforcement. Despite initial uncertainty, [13] it is now widely accepted that CBs also induce dopamine release in this region. This effect has been confirmed by neuroimaging work in humans,[14] and by neurochemical studies in rats,[7][15] following administration of natural and synthetic cannabinoids such as Δ^9-tetrahydrocannabinol (THC), the primary psychoactive chemical in marijuana and WIN-55212-2, respectively. We suggest that using dopamine release as a predictive metric of reinforcement/reward provides a distinction among CBs based on mechanism of action. Mainly, drugs that directly bind to and stimulate (i.e. direct agonists) CB1 receptors in the brain have greater effects on dopamine release than CBs that indirectly stimulate receptors (i.e. indirect agonists) by increasing levels of endogenous cannabinoids. Taken together, mesolimbic dopamine measurements provide a robust indicator of cannabinoid abuse liability and should be considered when determining which CBs exhibit a potential for abuse.

Introduction to the endogenous cannabinoid system

Although investigators initially isolated the principal psychoactive chemical in *Cannabis sativa*, Δ^9-tetrahydrocannabinol (THC),[16] in the 1960s, it was not until 1988 that they identified that THC binds to a G-protein coupled receptor in the brain.[17] This made way for the subsequent cloning of the cannabinoid CB1 receptor soon after,[18] and allowed for enormous progress in the characterization of the endogenous cannabinoid, or endocannabinoid (eCB) system. Cannabinoid receptors underlie an important component of intercellular signalling; expressed presynaptically, they are the most common G-protein coupled receptor in the mammalian brain[19] and modulate synaptic transmission by regulating release of other important signalling molecules such as GABA and glutamate.[20] Anandamide[21] and 2-arachidonoylglycerol (2-AG)[22] were the first, and remain the best, researched endogenous molecules that act upon cannabinoid receptors.

Despite binding to a common protein, the two endocannabinoids (eCBs) have different effects. While 2-AG has less affinity for CB1 receptors than anandamide, it exerts full agonism, whereas anandamide acts only as a partial agonist and binds to other non-cannabinoid receptors.[23] 2-AG is reported to be as much as 1000 times more concentrated in the brains of nonhuman primates[24] and is thought to play a more essential role in brain eCB neurotransmission.[24,25] Even abused substances influence these ligands independently, sometimes altering the concentration of one but not the other.[26] Importantly, 2-AG and anandamide are cleared from the extracellular space by different mechanisms, allowing for selective pharmacological enhancement of a single eCB without directly acting upon CB receptors or influencing the concentration of the other eCB. Some investigators have suggested that anandamide is selectively removed by a reuptake/transport mechanism, [27] but this remains contentious, as others have argued that 2-AG is also removed through this protein.[28] Recent advances in pharmacology however, allow us to independently

manipulate these two eCBs by targeting their distinct degradative enzymes. Extracellular anandamide is selectively metabolized by the enzyme fatty acid amide hydrolase (FAAH), and 2-AG is broken down by the enzyme monoacylglycerol lipase (MAGL). Thus, drugs can exert effects by directly binding to and acting upon cannabinoid receptors (direct agonism/antagonism), or by influencing proteins involved in reuptake or degradation (indirect agonism/antagonism). The distinction between these two mechanisms of drug action has important implications for the therapeutic potential and abuse liability of the compound.

Direct agonists increase dopamine and are associated with behavioural indices of abuse

THC and commonly abused synthetic CBs in K2 and Spice, such as or JWH-018,[4] are direct agonists. By binding directly to CB1 receptors, they 'hijack' normal eCB signalling and exert stimulation of these receptors, often in ways that are more potent than eCBs alone.[19] Moreover, synthetic CBs, despite having similar mechanisms of action as THC, frequently act with significantly higher potency.[19] Neurochemical experiments demonstrate that the direct agonists THC and WIN-55212-2 generally raise dopamine levels in the nucleus accumbens.[9] These general elevations in nucleus accumbens dopamine concentration are thought to arise from an increase in the mean firing rate of dopamine neurons within the ventral tegmental area. In support of this theory, reports indicate that direct CB agonists augment the firing rate of ventral tegmental area dopamine neurons.[29,30] For example, administration of HU210 (the most potent exogenous CB agonist) produces a robust increase in dopamine cell firing rate in the ventral tegmental area.[31] In addition to generally elevating dopamine concentrations and mean dopamine cell firing rates, CBs promote bursts of dopaminergic neural activity. These high-frequency (>20Hz vs. <5Hz) bursts produce sub-second surges of dopamine release in the nucleus accumbens that are sufficient to effect an otherwise inactive population of receptors (dopamine D1) in a manner thought to promote drug seeking.[32,33] For example, THC, WIN-55212-2 and CP 55940 increase the frequency of dopamine cell bursts[34] and the corresponding sub-second dopamine release events in the nucleus accumbens.[15] Taken together, ample data demonstrate that direct CB1 agonists fit the neurochemical profile of drugs that are rewarding/reinforcing.

Some behavioural data have corroborated these neurochemical findings, but studies often produce conflicting reports. For example, both WIN-55212-2 and THC increase heroin self-administration.[35] In addition, some studies have successfully demonstrated self-administration of these drugs in drug naïve non-human primates,[36] and rodents[37] using fixed-ratio schedules of reinforcement. We are, however, sceptical of exclusively using simple behavioural approaches rather than those that assess reinforcement strength (e.g. choice procedures, progressive ratio schedule, behavioural economics approaches). This is because behavioural assays frequently produce inconsistent results due to the difficulties associated with using CBs as reinforcers.[7,10] Even though researchers are beginning to identify specific experimental parameters that engender more consistent self-administration behaviour,[10,36] investigators have not yet applied behavioural economic approaches,[10] which more rigorously and precisely assess the reinforcing strength of a drug. We feel implementation of these paradigms is crucial to assess the abuse liability of CBs with self-

administration tests. Thus, neurochemical work currently is a more reliable metric of CB abuse liability than behavioural assays.

Indirect agonists, on the other hand, have considerably less abuse liability as demonstrated by effects on mesolimbic dopamine release

Selective enhancement of either 2-AG or anandamide, through disruption of reuptake mechanisms or inhibition of enzymatic degradation, is said to indirectly agonize CB receptors because the drugs do not themselves bind to receptors, but rather increase receptor stimulation by enhancing the concentration of the endogenous ligands. In this way, drugs that act through these indirect mechanisms act more selectively on a specific eCB. Moreover, eCBs are produced on demand and thus these drugs only act upon receptors in synapses where the eCB, is produced and released.[37,38] Direct agonists, in contrast, act anywhere a functional CB receptor is present.

Drugs that increase anandamide through inhibition of an uptake mechanism are not associated with neurochemical or behavioural indices of reward/reinforcement

For example, our lab has recently demonstrated that a drug that acts through this mechanism, VDM11, decreases cue-evoked dopamine release, nucleus accumbens neural encoding of reward-related cues and reward-directed behaviour.[39,40] Other neurochemical work has shown that inhibition of the eCB transporter with the drug AM404 is not associated with increased accumbal DA release under resting conditions[41] and even blunts nicotine-induced increases in dopamine.[42] A drug with the same mechanism, UCM-707, has similar effects to the CB1 receptor antagonist, rimonabant, on the firing rate of ventral tegmental area neurons following medial forebrain bundle stimulation, a response opposite to that produced by a direct CB1 agonist.[43] This finding is important because CB1 receptor blockade with rimonabant is associated with a reduction in reward-associated dopamine release,[39] suggesting that, if anything, certain classes of eCB uptake inhibitors function more like antagonists than direct agonists in the context of dopamine signalling.

These neurochemical findings are supported by behavioural work demonstrating that these drugs appear to lack the behavioural effects of direct CB1 agonists. The anandamide transport inhibitors, UCM-707 and AM404 are not associated with THC-like discriminative stimulus effects,[44] and lower self-administration of alcohol.[45] In general, inhibitors of anandamide transport exhibit distinct behavioural effects compared to direct CB1 agonists, [46] further distinguishing them from compounds like THC. It should be noted, however, that some investigators have also suggested that the transport mechanism these drugs act upon may be involved with both release and reuptake of both 2-AG and anandamide,[28] such that its inhibition results in a reduction of eCB release in general (indirect antagonism). Clearly, more research is required to settle this debate, but regardless of the pharmacological mechanism, there is considerable evidence suggesting that drugs of this nature exhibit no neurochemical indices of reward/reinforcement.

Likewise, drugs that enhance anandamide by blockade of the degradative enzyme FAAH, also appear to have minimal abuse liability

Neurochemical studies demonstrate that the FAAH inhibitor URB597 alone does not potentiate nucleus accumbens dopamine when administered under resting conditions,[44] nor does it have an effect on the firing rate of ventral tegmental area neurons following medial forebrain bundle stimulation.[43] Furthermore, URB597 prevents the nicotine-induced rises in dopamine levels in the nucleus accumbens[47] as well as mesolimbic dopamine neuronal firing rates.[48] This is corroborated by behavioural data as well. For example, URB597 is not self-administered[49] and does not generalize to THC in drug-discrimination procedures.[44] URB597 fails to enhance self-administration of cocaine or THC and is not sufficient to reinstate THC or cocaine seeking, suggesting these drugs could be used without triggering drug-seeking in addicts.[49] URB597 does not produce conditioned place preference. In fact, both anandamide transport and FAAH inhibition are associated with a reduction in heroin self-administration, an effect, as previously mentioned, that is in marked contrast to that of direct CB1 agonists.[35] Moreover, URB597 blocks behavioural markers of nicotine reward.[47] Indeed, FAAH inhibitors have been discussed as potential therapies for the treatment of cannabinoid[50] and nicotine addiction.[47] FAAH inhibitors also lack the undesirable behavioural characteristics associated with direct CB agonists, such as cataleptic and strong hypokinetic effects.[46] While we feel behavioural measures of reward must be interpreted with caution, their support of the neurochemical data adds to the rich body of evidence that indirect agonists of anandamide pose no abuse liability and instead demonstrate higher therapeutic potential.

Potentiation of 2-AG, via inhibition of its metabolizing enzyme MAGL, demonstrates similar neurochemical qualities despite a paucity of research on the subject

For example, prolonged application of JZL184, a MAGL inhibitor, by itself, did not increase firing rates of nucleus accumbens dopamine neurons, although it did allow sub-threshold doses of dopamine D1/D2 receptor agonists to increase firing rates of these cells.[51] Moreover, our lab recently showed that JZL184 selectively increased reward-directed behaviour and cue-evoked dopamine release.[39] We did not, however, observe any apparent increase in dopamine transient frequency from the drug alone, suggesting that the drug fails to produce a neurochemical signature of all known drugs of abuse, and may instead increase motivation for specific goal-directed tasks without posing abuse liability in its own right. Therefore, it could be of value for brain disorders involving blunted motivation. While the current literature addressing its dopaminergic effects suggests that these compounds possess little abuse liability, more research is required to characterize the neurochemical effects of drugs that act through this mechanism. Although evidence suggests that methanandamide, the metabolically stable analogue of anandamide,[44] and 2-AG may have some rewarding/reinforcing effects,[52] this does not indicate that inhibitors of FAAH, the anandamide transport, or MAGL share these qualities. As previously mentioned, these drugs only act in synapses where eCBs are already produced, but administration of 2-AG or anandamide (methanandamide) acts on the whole CB receptor reserve.[37,38]

Cannabinoid agonists, in general, have the potential for the treatment of drug addiction, anxiety, cancer and pain

Both direct and indirect CB receptor agonists have high medicinal value in the realm of acute and chronic pain.[53,54] Indeed, the significant cross-talk between opioid and eCB systems might expand the therapeutic window to treat pain.[10,55] For example, opioids and CBs have a synergistic effect when used together.[56] Direct CB receptor agonists as well as drugs that inhibit MAGL and FAAH induce analgesia and attenuate inflammation in animal models, but more research is required to determine specifically where in the brain these drugs might be useful, as some results are still conflicting.[54] In addition, direct CB receptor agonists as well as blockade of FAAH and MAGL reduce behavioural signs of opioid withdrawal.[57] The use of indirect agonists has also been proposed for the treatment of marijuana withdrawal, since it lacks many of the behavioural effects associated with direct CB agonists, while also alleviating withdrawal symptoms by stimulating CB activity where appropriately released.[46] This could be thought of as a weak agonist treatment, much in the same way buprenorphine is used for the treatment of heroin. As mentioned, these indirect agonists attenuate markers of reward from nicotine,[47] and alcohol.[45] Although CB antagonists such as rimonabant have been proposed for the treatment of compulsive disorders, indirect agonists appear to be superior because they lack the depressive effects associated with CB1 receptor blockade.[58] In fact, FAAH[46] and MAGL inhibition decrease behavioural signs of anxiety and possess anti-depressant effects.[58] Finally, both direct and indirect agonists have strong potential for the treatment of numerous cancer types, including but not limited to bone, breast and prostate cancer.[59] Given that CBs that have currently been synthesized show such promising and diverse therapeutic potential suggests that more work should be done into studying these drugs' medicinal properties.

Conclusion

Taken together, CB receptor agonists exhibit high therapeutic potential for the treatment of pain, anxiety, cancer, and drug addiction, and indirect agonists, specifically, exhibit low potential for abuse. Mesolimbic dopamine recordings provide a robust marker of abuse liability that can be used in spite of the inconsistency of studies that employ behavioural indices of cannabinoid reward/reinforcement. Indeed, neurochemical work demonstrates that many of the CB receptor agonists recreationally used by the population do in fact increase dopamine release and pose a potential for abuse. Review of neuroscientific research should be closely examined when designing drug policy, given that prohibition of substances can hinder research and pharmaceutical development.

If regulatory bodies feel that it is necessary to permanently regulate the direct CB receptor agonists currently under review, they should do so within the Schedule II category. This will effectively acknowledge the medicinal properties of all cannabinoids and allow for fewer restrictions on their use in medical and research environments. Moreover, it will specifically allow for compound-by-compound decisions to be made under the basis of whether a drug is a safe and effective medicine as opposed to unilaterally banning its use. Policies that treat indirect agonists and direct agonists similarly ignore the medicinal benefits and low abuse liability of indirect agonists, and should thus be avoided. Any potential regulation of direct

CB1 agonists should be explicit as it can potentially influence the use of indirect CB1 agonists in laboratories and medical environments, since federal scheduling could effectively enact bans of indirect agonists due to the analogue act. Even if the analogue act does not result in a functional ban of other compounds with similar mechanisms of action and federal scheduling does not explicitly ban CB receptor agonists that investigators use, state regulation may hinder research. Many investigators of the eCB system conduct neuropharmacology research, but do have DEA licenses. When such labs are located in states with general CB agonist bans, they are explicitly inhibited in their contributions to the elucidation of this important signalling system. Indeed, Dr John Huffman (Clemson University), creator of the initial synthetic CB agonists has stressed that despite potential adverse effects of CB abuse, there is a general worry among researchers that strict regulation of these compounds will impede upon research into the effects of exogenous CBs, as well as the eCB system, in general.[4] Indeed, any regulation that bans ligands that target the most common G-protein coupled receptors in the mammalian brain will surely impede upon research and insights into the functioning of the nervous system.

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