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Tales from the dark side: do neuromodulators of drug withdrawal require changes in endocannabinoid tone?

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Abstract

Environmental and interoceptive cues are theorized to serve as ‘signals’ that motivate drug seeking, effects that may be augmented in the withdrawn state. Phasic dopamine release events are observed in the nucleus accumbens in response to such motivational salient stimuli and are thought to be necessary for drug-associated cues to trigger craving. We recently demonstrated how dopamine neurons encode stimuli conditioned to a negative event, as might occur during conditioned withdrawal, and stimuli predicting the avoidance of negative events, as might occur as an addict seeks out drugs to prevent withdrawal. In this review we first discuss how the subsecond dopamine release events might process conditioned withdrawal and drug seeking driven by negative reinforcement processes within the context of our dopamine data obtained during conditioned avoidance procedures. We next describe how the endocannabinoid system modulates phasic dopamine release events and how it might be harnessed to treat negative affective states in addiction. Specifically, we have demonstrated that endocannabinoids in the ventral tegmentum sculpt cue-induced accumbal surges in dopamine release and, therefore, may also be mobilized during drug withdrawal.

Keywords

Addiction; dependence; endocannabinoid; dopamine; avoidance

1.1. Introduction

Negative reinforcers, or events that increase the probability of behavioral actions resulting in the escape or avoidance of the particular event, are thought to play a prominent role in drug addiction. By recruiting neural pathways that process negative reinforcement, drug

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withdrawal is theorized to produce a negative emotional state—capable of driving persistent drug seeking (Childress et al. 1988, Koob et al, 1998). While traditionally thought to be specific to drugs producing explicit somatic withdrawal symptoms, like opiates and alcohol, it is now recognized that all drugs of abuse produce some form of withdrawal.

1.2. Evidence for drug withdrawal

Drug withdrawal subsists in the absence of overt symptomatology (e.g., delirium tremens). For example, Wood and Lal (1987) used drug-discrimination to demonstrate that cocaine withdrawal is anxiogenic in nature. In their early behavioral pharmacological work, rats were trained to respond on one of two levers for food pellets under an FR10 reinforcement schedule after either receiving injections of the anxiogenic drug pentylenetetrazol or in the absence of any drug effect. They then tested to see whether the subjective effects of cocaine withdrawal generalized to those produced by pentylenetetrazol by treating rats with cocaine (20mg/kg IP) every 8 hours for 7 days, and then assessing lever selection after 8, 24, 96, 120 and 148hrs of forced abstinence. They found that the withdrawal effects of cocaine generalized to the pentylenetetrazol stimulus effects, as animals increasingly selected the pentylenetetrazol-paired lever over the first 120 hrs of abstinence. While this study demonstrated that cocaine withdrawal is anxiogenic in nature, it is important to note that the reported withdrawal effects were devoid of somatic symptoms, such as: diarrhea, wet-dog shakes, weight loss, teeth chattering, tremors and convulsions (Wood and Lal, 1987). Clinical studies corroborated the existence of a cocaine withdrawal syndrome, characterized by anxiety and sleep disturbances (Gawin, 1991; Watson et al. 1992). Another classic example are the cannabinoids (e.g., marijuana), a drug class long thought to be devoid of withdrawal symptoms (Solomon and Corbit, 1974). While spontaneous withdrawal symptoms are difficult to detect in experimental animals (Aceto et al. 1996, Aceto et al. 2001), pronounced somatic withdrawal symptoms (e.g., wet dog shakes, paw tremors) are inducible by challenging dependent animals with a cannabinoid CB1 receptor antagonist (Aceto et al., 1995; Tsou et al., 1995). Clinical studies further described a spontaneous cannabis-withdrawal syndrome, characterized by: anxiety, weight loss, restlessness, sleep problems, chills, depressed mood, physical discomfort, shakiness, and sweating (Budney and Hughes, 2006). Together, these preclinical and clinical reports indicate that the majority of abused drugs are capable of producing some form of withdrawal.

2.1. Conditioned withdrawal

Through Pavlovian conditioning, interoceptive (e.g., subjective effects) and exteroceptive (e.g., sights, sounds, smells or situations) cues become associated with withdrawal symptoms and act cumulatively to motivate drug seeking. Indeed, conditioned withdrawal is such a strong force in drug addiction, it was one of the earliest factors noted by the medical community (Wikler, 1973) and continues to be considered a critical feature in addiction by today's leading psychiatrists (O'Brien et al., 2009).

2.2. Conditioned withdrawal: interoceptive effects

Subjective effects produced by drug withdrawal increase over periods of abstinence (Wood and Lal, 1987) and may contribute to the increased drug seeking ('incubation') that is

observed over a course of weeks in reinstatement self-administration models of addiction (Tran-Nguyen et al. 1998, Grimm et al. 2001, Lu et al. 2004). Consistent with this supposition, Wang and colleagues (2013) recently reported that the conditioned peripheral effects of cocaine are sufficient to increase drug seeking over time in rats withdrawn from cocaine (Wang et al. 2013). It has been theorized that these conditioned interoceptive drug effects and negative affect play off of each other to produce even stronger motivational influences on drug craving (Childress et al. 1988, Baker et al. 2004). The concept that negative affect itself conjures up withdrawal symptoms and produces drug craving is supported by studies involving hypnotically induced states of depression. In these studies it was found that hypnotically inducing a state of depression in detoxified drug addicts led to the emergence of conditioned withdrawal symptoms and drug craving (Childress et al. 1987, Childress et al. 1994).

2.3. Conditioned withdrawal: exteroceptive effects

Withdrawal associated exteroceptive cues also play a prominent role in the addiction phenomenon. Extensive clinical studies demonstrating the power withdrawal associated exteroceptive cues hold over drug craving and drug seeking exist (O'Brien, 1975, 1977, Childress et al. 1986a, 1986b, 1988). Recent advances in neuroimaging have allowed experimenters to expand upon these initial behavioral and physiological observations to indentify the neural substrates involved in cue-induced drug craving (Childress et al. 1999, Volkow et al. 2006, 2008). Of note, these studies demonstrate that rapid surges in dopamine release within the striatum are necessary for drug-associated cues to trigger craving (Volkow et al. 2008).

3.1. Relating conditioned avoidance to conditioned withdrawal

We recently demonstrated that rapid surges in dopamine release within the ventral striatum encode stimuli during conditioned avoidance (Oleson et al. 2012a) and believe these data provide novel insight into how the brain processes conditioned withdrawal. The parallels between this signaled footshock avoidance procedure and conditioned withdrawal have been described in detail elsewhere (Baker et al. 2004). Briefly, Baker and colleagues recognized that conditioned avoidance exemplifies the sort of motivational processes that are theorized to motivate addictive behavior during drug withdrawal and further point out that conditioned avoidance incorporates the primary elements involved in conditioned withdrawal—namely exteroceptive cues (e.g., warning signals indicate that shock is avoidable) and subjective responses (e.g., negative affective state; fear).

3.2. Conditioned avoidance methodology

To investigate whether dopamine encodes cues during conditioned avoidance, we used fast-scan cyclic voltammetry to measure dopamine concentration transients in the ventral striatum (specifically the nucleus accumbens core) while rats behaved in an operant signaled foot shock avoidance procedure. In this task, a cue light was presented as a warning signal for 2s prior to the delivery of recurring foot shocks. During this 2s warning period, a response lever extended into the operant chamber which, if depressed, produced a 20s safety period signaled by a tone. Rats initiated an avoidance response by pressing the lever within

the 2s warning period, thus entirely preventing shock. Alternatively, rats initiated an escape response by pressing the lever after shocks commenced, thus terminating ongoing shock. This experimental design allowed us to assess dopamine signaling during warning signal presentation, safety periods and during two distinct behavioral responses—avoidance and escape. Animals received extensive training (~15-25 sessions) and exhibited >50% avoidance before recording sessions commenced.

3.3. Conditioned avoidance and dopamine

We (Oleson et al. 2012a) found that dopamine concentration transients rapidly increased upon presentation of the warning signal (Figure 1A, first peak) in a manner that predicted when animals successfully avoided foot shock, as the concentration of cue-evoked dopamine release remained significantly higher in avoidance versus escape trials. We also observed rapid increase in dopamine concentration transients during the safety period (Figure 1B, second peak). These data demonstrate that subsecond dopamine release accompanies cues predicting negative reinforcement. Regarding a parallel to the addiction phenomenon, as previously suggested (Baker et al. 2004), we infer that dopamine neurons encode the warning signal similarly to an environmental cue directing an animal toward the relief of withdrawal (i.e., drug availability) and the safety signal similarly to an animal taking drug to relieve negative affect (Baker et al. 2004).

Additional conditioned place aversion and drug self-administration studies provide strong evidence for dopaminergic involvement in the avoidance of negative affect during drug withdrawal. In general, dopamine receptor antagonists reduce the conditioned aversive effects associated with opiate (Bechara et al. 1992, Nader K et al. 1994, Nader and Van der Kooy, 1997) and nicotine (Grieder et al., 2010) withdrawal; whereas, dopamine receptor agonists administered during opiate withdrawal enhance behavioral activation and drug seeking (De Vries et al. 2002, Druhan et al. 2000). Intriguingly, dopamine receptor antagonism, or lesions that alter mesolimbic dopamine function, exclusively modulate the conditioned reinforcing effects of opiates in animals that received a sufficient pharmacological history to render them in a chronic state of deprivation, or dependence (Bechara and Van der Kooy, 1992, Nader et al. 1994). The observation that dopamine exclusively modulates conditioned aspects of opiate reinforcement in dependent rats led Derek Van der Kooy and colleagues to identify a ‘switch’ within the ventral tegmental area that may explain an enhanced role for dopamine in withdrawal. Specifically, these investigators demonstrated that GABA_A receptors within the ventral tegmental area switch from an inhibitory to an excitatory signaling mode when dependent animals are deprived from opiates (Laviolette et al. 2004). As the role of dopamine in the conditioned reinforcing effects associated with various reinforcers, even food (Bechara and Van der Kooy, 1992), depends on the state of the organism, it is tempting to speculate that the nondeprived/deprived “switch” model pertains to various experimental and clinical conditions involving lengthy histories of negative affect. But how might dopamine neurons encode stimuli that actually represent negative affect?

3.4. Conditioned fear and dopamine

In 2012 two concurring reports described how dopamine concentration transients encode cues associated with the negative emotion of fear (Badrinarayan et al. 2012, Oleson et al. 2012a). This was accomplished using standard fear conditioning approaches. For example, Oleson et al. (2012a) initially presented rats with three consecutive tones (20-s; ITI 3-min), each culminating with a 2-s foot shock and then, 24-hr later, presented them with 18 iterations (20-s tone, inter-trial-interval 3-min) of the conditioned tone alone in a novel context. Freezing behavior was assessed every 5-s by a blind experimenter and dopamine measurements were made every 100-msec using fast-scan cyclic voltammetry. Using this approach it was found that dopamine levels decreased in the nucleus accumbens core for the duration of the fear associated stimulus (Figure 1B) in trials in which the tone induced a conditioned freezing response (Badrinarayan et al. 2012, Oleson et al. 2012a). From these observations, we infer that dopamine neurons may encode the fear-associated cue similarly to the negative affect induced by conditioned drug withdrawal.

Recent evidence suggests that dopamine may play a functional role in the generation of behavioral responses to negative affect by influencing whether an animal freezes or exhibits a directed action sequence. Subsecond dopamine concentrations are theorized to modulate converging hippocampal, cortical and amygdalar input within the striatum (Floresco et al. 2001, Brady and O'Donnell, 2004). The modulatory role of amygdalar input, in particular, is likely of critical importance in behavioral responses driven by negative affect, as it is well known that the amygdala is necessary for both the expression of conditioned withdrawal (Schulteis G et al. 2000) and conditioned fear (Davis, 1992, Morgan and LeDoux, 1995). According to the canonical role of the basal ganglia in the generation of action sequences, high concentration dopamine transients are thought to promote behavioral activation by activating striatal D1 expressing medium spiny neurons comprising a direct pathway, while decreases in dopamine release may inhibit behavior by activating striatal D2 expressing medium spiny neurons comprising an indirect pathway (DeLong and Wichmann, 2007). A recent optogenetic study revealed that selective stimulation of the direct pathway promotes behavioral activation, while selective stimulation of striatal dopamine D2 receptor expressing neurons of the indirect pathway promotes freezing behavior (Kravitz et al. 2010), thereby suggesting that dopaminergic modulation of striatal neural activity may play a functional role in the manifestation of distinct behavioral responses during negative reinforcement and conditioned withdrawal.

3.5. Big picture: relating dopamine in conditioned fear and conditioned avoidance to addiction

Our observation that increased dopamine release occurs during the safety period suggests that this is encoded similar to a primary reward (Oleson et al. 2012a, for review see Oleson and Cheer, 2013). Through the progression of addiction however, fear may begin to dissipate as the experienced addict learns how to efficiently avoid negative affect; likewise, in avoidance learning, fear responses such as freezing begin to dissipate throughout training (Oleson et al. 2012a, for review see Oleson and Cheer, 2013). During this transition we hypothesize that dopaminergic encoding of the warning signal switches, from a pause in

release that represents fear to a surge in release that represents the confident relief of negative affect. Finally, as compulsive addictive behavior is established, conditioned stimuli become more potent motivators of behavior than their representations (e.g., relief of withdrawal) through higher order conditioning.

3.6. Negative affect, brain reward function and dopamine

All aforementioned data involve the role of subsecond dopamine release events, presumably arising from burst firing of A10 dopamine neurons (Sombers et al. 2009), in modulating conditioned avoidance and conditioned fear. Although many excellent reviews already exist on the topic (Koob and Volkow, 2010; Spanagel and Weiss, 1999; Kenny, 2007), it is worth noting that a substantial amount of experimental work has detailed changes in tonic dopamine concentration and brain reward function within the context of drug withdrawal. In vivo microdialysis studies reveal that decreased tonic dopamine concentrations are reduced in the ventral striatum of experimental animals during withdrawal from various drugs of abuse (Rossetti et al. 1992; Weiss et al. 1992; Weiss et al. 1996). Corresponding decreases in brain reward function are observed during conditioned withdrawal when assessed using intra-cranial self-stimulation (Kenny et al. 2006). These decreases in tonic dopamine concentration and brain reward function are also theorized to contribute to the negative affect accompanying drug withdrawal.

4.1 Endocannabinoids modulate subsecond dopamine release

The endocannabinoid system, composed of lipid signaling molecules (2-arachidonoylglycerol and anandamide were the first and remain the best characterized endocannabinoids), their G protein-coupled receptor targets (CB1 and CB2), synthesizing enzymes (diacylglycerol lipase; N-arachidonoyl phosphatidylethanolamine phospholipase D), hydrolyzing enzymes (monoacylglycerol lipase and fatty acid amide hydrolase), and a putative transport system (Fu et al. 2011), plays a regulatory role on dopamine signaling during behavior (Lupica and Riegel, 2005; Solinas et al. 2008), especially behavior under the control of conditioned stimuli (Le Foll and Goldberg, 2004; De Vries and Schoffelmeer, 2005). The observation that endocannabinoid manipulations are especially potent at regulating cue-motivated behavioral responses (Le Foll and Goldberg, 2004; De Vries and Schoffelmeer, 2005) may be due, in part, to the synthesis and release of endocannabinoids resulting from the phasic activation of dopamine neurons (Freund et al. 2003; Melis et al. 2004) induced by the presentation of a motivational salient cue (Oleson et al. 2012b). In contrast to other neuromodulators (e.g., dopamine), endocannabinoid synthesis and subsequent release is triggered by activation of $G_{q/11}$ -coupled metabotropic receptors and/or postsynaptic depolarization (Freund et al. 2003). When neurons fire in high frequency bursts, voltage gated Ca^{2+} channels open allowing for an influx of Ca^{2+} that, in turn, activates the enzymes responsible for endocannabinoid synthesis (Wilson and Nicoll, 2002). Non-vesicular release of endocannabinoids from the postsynaptic domain results in activation of the presynaptic CB1 receptor, which is mainly coupled to G_i . In turn, G_i activation modulates presynaptic K^+ and Ca^{2+} conductances leading to a reduction of neurotransmitter release (reviewed by Freund et al. 2003; Cachope, 2012). Since CB1 activation has been shown to increase dopamine neuronal firing and release (French, 1997;

French et al. 1997; Cheer et al. 2004), several potential mechanisms have been proposed to explain this effect, including a direct stimulatory action on dopaminergic neurons, an indirect enhancement of excitatory activity, and a reduction of inhibitory activity (Szabo et al. 2002). However, endocannabinoids are unable to directly modulate dopamine neurons through a CB1 receptor dependent mechanism, as midbrain dopamine neurons lack cannabinoid CB1 receptors, (Mailleux and Vanderhaeghen, 1992; Matsuda et al., 1993; Julian et al. 2003). Furthermore, dopamine release is not mediated by a direct effect of cannabinoids on dopaminergic terminals (Szabo et al. 1999). Instead, increasing evidence exists for a mechanism known as disinhibition, in which activation of CB1 receptor inhibits GABAergic transmission in the VTA, lessening the inhibitory break on dopamine neurons (Szabo et al. 2002; Cheer et al. 2000; Lupica and Riegel, 2005). In this model, endocannabinoid (presumably 2-AG (Matyas et al. 2008; Tanimura et al. 2010)) activity on CB1 receptor promotes reduction of GABAergic input onto dopamine neurons in the VTA leading to an increased rate of neuronal firing and subsequent enhancement of dopamine release in the nucleus accumbens (reviewed by Melis and Pistis, 2012).

4.2 Endocannabinoids, dopamine and conditioned withdrawal

As previously described, the cue-evoked increases in dopamine release observed during the avoidance of negative stimuli may play a prominent role in the addiction process. As such, disrupting endocannabinoid neurotransmission may effectively diminish the power that drug-associated cues exert over dopamine release when in the withdrawn state, and even during instances of conditioned withdrawal in the drug-free state. We recently demonstrated that disrupting endocannabinoid signaling by pretreating rats with cannabinoid CB1 receptor antagonists decreases dopamine release evoked by drugs of abuse (Cheer et al. 2004) and conditioned predictors of positive reinforcement (Oleson et al. 2012b). Future studies will assess whether disruptions in endocannabinoid signaling also reduce dopamine release evoked by cues predicting negative reinforcement (i.e., conditioned avoidance). If it is found that disrupting endocannabinoid signaling effectively reduces cue-evoked dopamine release during negative reinforcement, such pharmacotherapies may be used to assuage the drug craving occurring during conditioned withdrawal (Figure 2). We would like to point out that, due to the clinical dangers previously encountered with the use of the CB1 receptor antagonist rimonabant (Hill Gorzalka, 2009), future lines of research involving cannabinoid receptor antagonists should be approached with caution. However, advances in our understanding of the endocannabinoid system and the consequent development of new pharmacological tools may allow for safer alternatives (e.g., neutral competitive antagonists, partial agonists that might compete with 2-arachidonoylglycerol, DGL- α inhibitors, etc.).

4.3 Endocannabinoids, dopamine and negative affect

Alternatively, pharmacologically increasing endocannabinoids may provide a relatively safe substitution therapy during stages of the addiction process in which negative affect is a primary motivator of behavior. Based on fear conditioning data (Oleson et al. 2012a), we predict that the negative affect occurring during drug withdrawal would be accompanied by a decrease in subsecond dopamine release events. Thus, facilitating endocannabinoid modulation of dopamine release may normalize the short lasting decreases in dopamine

release that we, and others, theorize are associated with negative affect (McCutcheon et al. 2012, Oleson and Cheer. 2013, Roitman et al. 2008).

4.4 Increasing endocannabinoid tone produces anti-withdrawal effects

It has long been recognized that exogenous cannabinoids offer therapeutic utility in the treatment of addictions that are characterized by potent withdrawal symptoms. For example, in the first volume of the medical journal the *Lancet*, a case report concluded that cannabis substitution for opiate dependence markedly improved the quality of life (Birch, 1889). However, the abuse liability associated with drugs like marijuana may limit their therapeutic utility. Even in the early case report by Birch (1889) he cautioned that, “I would insist the necessity of concealing the name of the remedial drug from the patient, lest in his endeavor to escape from one for vice he should fall into another.” Alternatively, elevating endocannabinoid tone provides an approach to treat withdrawal symptoms without posing great risk for potential for abuse (Loewinger et al. 2013). The Lichtman group has conducted several studies to test whether increasing specific endocannabinoids might reduce opiate withdrawal symptomatology. They found that increasing anandamide reduces a subset of withdrawal symptoms (Ramesh et al. 2011), increasing levels of 2-arachydonoylglycerol reduces all withdrawal symptoms but may produce cannabimimetic effects (although the mesolimbic system may be spared; (Ramesh et al. 2011, Long et al. 2009), and simultaneously increasing anandamide and 2-arachydonoylglycerol reduced all withdrawal symptoms without the detection of cannabimimetic effects (Ramesh et al. 2013). These anti-withdrawal effects may be partially attributed to endocannabinoid action within the amygdala. Indeed, a recent translation study demonstrated that facilitating anandamide function within the amygdala diminishes stress reactivity across species, from mice to man (Gunduz-Cinar et al. 2013). This finding is consistent with the well-accepted notion that the amygdala endocannabinoid system is critically involved in the expression of fear memories (Marsicano et al. 2002) and generally functions to attenuate anxiety (Lutz, 2009). It may not be surprising, therefore, that anandamide’s degradative enzyme, FAAH, is reduced during alcohol withdrawal (Rubio et al. 2008, Serrano et al. 2012), while FAAH inhibition diminishes the anxiogenic response observed during alcohol or nicotine withdrawal (Cippitelli et al. 2008, Cippitelli et al. 2011). A recent study also reported that 2-arachydonoylglycerol’s degradative enzyme (MAGL) can also be reduced, but only following repeated withdrawals induced by intermittent alcohol exposure (Serrano et al. 2012).

5. Conclusions

We recently demonstrated that subsecond dopamine release events encode conditioned cues during behaviors driven by negative reinforcement, and that these subsecond dopamine release events are critically modulated by endocannabinoid signaling (Oleson et al. 2012a, 2012b). Understanding the neural mechanisms underlying these dopaminergic changes may offer novel insights into drug addiction, as avoidance from drug withdrawal is thought to promote compulsive drug seeking. Developing a better understanding of how endocannabinoids modulate dopaminergic encoding of cues during negative reinforcement

will be critical to assess whether endocannabinoid pharmacotherapies may be useful in the treatment of drug addiction.

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Highlights

- All drugs of abuse produce some form of withdrawal
- Withdrawal-associated stimuli begin to motivate drug seeking
- Conditioned withdrawal shares parallels with conditioned avoidance
- Subsecond dopamine release is involved in conditioned avoidance
- Endocannabinoids have the potential to modulate subsecond dopamine release during drug withdrawal

Figure 1.

A) Dopamine encodes conditioned stimuli during an avoidance response. The dopamine concentration trace is centered on warning signal presentation (represented by dashed line with light) and plotted as a function of time. B) Dopamine encodes conditioned stimuli during a fear response. The dopamine concentration trace is centered on tone presentation (gray bar) and plotted as a function of time.

Figure 2.

Pictorial showing pharmacological interventions that might inhibit 2-arachidonoylglycerol facilitation of dopamine signaling during negative reinforcement. General picture: As animal is cued to seek reinforcement (negative or positive), increased glutamate release into the ventral tegmental area results in the activation of A10 dopamine neurons. As a result, increased intracellular Ca^{2+} activates the enzyme responsible for the synthesis of 2-arachidonoylglycerol, diacylglycerol lipase- α , which hydrolyzes diacylglycerol to form 2-arachidonoylglycerol. 2-arachidonoylglycerol then crosses the plasma membrane where it can retrogradely activate CB1 receptors. 2-arachidonoylglycerol binding to CB1 receptors located on GABA terminals suppresses GABA release, ultimately disinhibiting the dopamine neuron and theoretically driving the animal to escape a negative situation (e.g., withdrawal state). As we are still in a discovery phase regarding the endocannabinoid system, it is likely that better pharmacological approaches to target the endocannabinoid system will continue to be developed. However, we highlight several approaches that could be implemented to decrease 2-arachidonoylglycerol facilitation of dopamine release. A) specific inhibitors of diacylglycerol lipase- α would decrease synthesis of 2-arachidonoylglycerol, B) competitive antagonists for the CB1 receptor (note: neutral competitive antagonists might produce more favorable clinical outcomes than rimonabant

because they lack inverse agonist effects, C) partial agonists may compete with 2-arachidonoylglycerol without producing negative effects associated with antagonists like rimonabant. Adapted from Lee et al. 2012.