The role of the endocannabinoid system in attention and nicotine addiction

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Abstract

The endocannabinoid system is a retrograde synaptic messenger system in many areas of the brain. Among other areas endocannabinoids have been shown to be important in the regulation of transmission in the VTA and dopaminergic reward pathways of the brain. These areas have also been shown to be implicated in mechanisms of addiction and addiction related behaviours. Nicotine is a highly addictive substance which works on the dopaminergic reward pathways of the brain. In this thesis we will explore the interaction and link between nicotine action in the VTA and endocannabinoid modulation of this action, and how this relates to addition. There is also some evidence that suggests that nicotine may facilitate certain aspects of cognition such as attention, while evidence suggests that cannabinoids impede it. We will therefore further explore if there is a relation between these two with respect to attention, and whether nicotine's action on attention is related to its addictive potential.

Introduction

Nicotine smoking is a major problem and is associated with major health issues and significantly elevated mortality rates (McGinnis and Foege, 1993). Nicotine is one of the most prevalently used addictive substances and is associated with low levels of cessation success. Extensive research is done into the neurobiological mechanisms underlying nicotine addiction. Recently, the endocannabinoid (eCB) system has gained interest as a possible new therapeutic target for treatment of nicotine addiction. Current research suggests that the eCB system can modulate the effects of various addictive drugs on the dopaminergic reward pathway. Through this modulation of the effects of drugs, the eCB system can modulate drug seeking behaviours and the rewarding and reinforcing properties of drugs. There is also emerging evidence that the eCB system and nicotine interact with respect to their effects on brain mechanisms providing further impetus into research examining the potential for the modulation of the eCB system in the treatment of nicotine addiction.

There are indications that nicotine exerts an effect on attentional processes, and that attention may be related to its addictive potential. In particular, individuals with low baselines of attentional levels are thought to be at elevated risks to nicotine addiction. The eCB system may be implicated in the modulation of these attentional processes. Given the link found with respect to nicotine addiction and this system, there is a possible role for the eCB system in modulating the effects of nicotine on attention.

The present paper aims to review studies demonstrating the role of the eCB system in nicotine addiction and the involvement of this system, and the influence of nicotine, on attentional processes. We will examine both the link between attention and nicotine addiction and the possible role that the eCB system may play in modulating this interaction. Therefore, the following aspects will be reviewed in subsequent sections:

i. How is the eCB system involved in mediating nicotine's addictive potential
ii. How is the eCB system involved in regulating attentional control and what is the influence of nicotine on attentional processing
iii. Is the possible link between the eCB system and nicotine in the modulation of attentional processing relevant to processes involved in nicotine addiction

To answer these questions, literature that has examined the localisation, functional roles, and mechanisms of the eCB system will be reviewed. A brief introduction to the mechanisms that are thought to underlie addiction in general will then be provided, before reviewing mechanisms of nicotine action and addiction in particular. Subsequently, a discussion of the possible involvement of the eCB system in nicotine addiction will be provided. In the third section of this thesis we will examine the possible involvement of the eCB system, and the influence of nicotine, in attentional processes. We will conclude with a discussion of the possible links between attention and nicotine addiction and investigate the possible role of the eCB in mediating this link.

The endocannabinoid system

At least two cannabinoid receptors have been identified: CB1 and CB2. Of these, CB1 is mainly located in the central nervous system while CB2 is located in the periphery. The CB1 receptor is located at the nerve terminals of neurons (Devane et al., 1988; Herkenham et al., 1991b; Howlett et al., 1990) and is the most abundant G-protein coupled receptor in the brain (Herkenham et al., 1991b; Howlett et al., 1990). The most important endogenous cannabinoid ligands binding to these receptors are anandamide (AEA) and 2-arachidonylglycerol (2-AG) (Devane et al., 1992; Mechoulam et al., 1995; Sugiura et al., 1995). AEA is released after neuronal depolarisation or receptor stimulation (Giuffrida et al., 1999; Kim et al., 2002; Stella and Piomelli, 2001). Termination of signalling of these two endogenous cannabinoids is mediated by reuptake of these molecules and subsequent hydrolysis (Cravatt et al., 1996). The hydrolysis of these endocannabinoids is performed by two enzymatic systems. Monoacylglyceride lipase (MAGL) is distributed in the nerve terminals of specific brain neurons and is mainly responsible for the degradation of 2-AG (Dinh et al., 2002; Gulyas et al., 2004). Fatty acid amide hydrolase (FAAH) is mainly responsible for the degradation of AEA, however it is also able to degrade 2-AG (Cravatt et al., 1996).

CB1 receptors are located throughout the whole brain with particular high densities reported in the hippocampus and certain nuclei of the basal ganglia (Bisogno et al., 2003; Rodriguez de Fonseca et al., 1998). In particular, endocannabinoids have been reported to be important in the regulation of the Ventral Tegmental Area (VTA) synaptic transmission (Matyas et al., 2008), consequently affecting the regulation of the mesocorticolimbic dopamine reward system (Gardner and Vorel, 1998; Lupica et al., 2004; Lupica and Riegel, 2005; Matyas et al., 2008; Riegel and Lupica, 2004). Additionally, CB1 receptors are also reported to be important in signalling in the striatum and substantia nigra (French et al., 1997; Herkenham et al., 1990; Herkenham et al., 1991a; Uchigashima et al., 2007). A robust finding concerning the expression of endocannabinoids in the striatum is the observation that they are involved in regulating the activity of the nucleus accumbens (NAcc) (Maldonado and Rodriguez de Fonseca, 2002; Robbe et al., 2002). For further detailed reviews on the brain localisation of endocannabinoids, see (Bisogno et al., 1999; Breivogel and Childers, 1998; Herkenham et al., 1990; Herkenham et al., 1991b).

The CB1 receptor is generally located presynaptically throughout the brain (Freund et al., 2003). The signalling molecules have been found to be synthesised on postsynaptic terminals and act on presynaptic CB1 receptors as retrograde synaptic messengers and serve to modulate the release of a number of different neurotransmitters (Melis et al., 2004b; Piomelli, 2003; Riegel and Lupica, 2004). The degradation enzymes show a close co-localisation to CB1 receptors indicating that they closely regulate eCB signalling. Whereas FAAH is located postsynaptically, MAGL is located presynaptically (Dinh et al., 2002).The difference in the localisation of these degradation enzymes suggests that 2-AG and AEA signalling may serve different functional roles. Endocannabinoids are not exclusively released in a depolarisation dependent and spatially unrestricted manner, but rather, are released under certain circumstances within certain types of synapses (Melis et al., 2004a; Melis et al., 2004b; Riegel and Lupica, 2004). The distribution of endocannabinoids on the neuronal terminals of cholinergic, GABAergic and glutamatergic neurons points to a role of the eCB system in modulating both the excitatory and inhibitory inputs to postsynaptic neurons (Cheer et al., 2000; Melis et al., 2004b; Riegel and Lupica, 2004; Szabo et al., 2002). Activation of CB1 receptors results in a local hyperpolarisation (Rodriguez de Fonseca et al., 2005). When located presynaptically, this will result in an inhibition of neurotransmitter release. If the eCB receptors are located on GABAergic neuronal terminals, receptor stimulation will result in a depolarisation-induced suppression of inhibition, and consequently reduce inhibitory inputs to the post-synaptic neuron. Conversely, if the receptors are located on glutamatergic synapses stimulation will result in a depolarisation-induced suppression of excitation (Diana et al., 2002; Wilson et al., 2001; Wilson and Nicoll, 2001). Furthermore, eCB signalling has been shown to be involved in the induction of long-term potentiation in hippocampal

synapses, (Stella et al., 1997) and facilitation of long term depression in the striatum (Gerdeman et al., 2002) and NAcc (Robbe et al., 2002). Overall, endocannabinoids "act as local [retrograde] messengers that adjust synaptic weight and contribute significantly to the elimination of information flow through specific synapses in a wide range of time frames." (pp.9, Rodriguez de Fonseca et al., 2005). For an overview of the processes involved in eCB retrograde transmission see figure 1 below.

Due to its expression in a number of different brain areas and its interactions with virtually all neurotransmitter systems (Ameri, 1999; Chaperon and Thiebot, 1999), the eCB system is implicated in a variety of different cognitive functions. Endocannabinoid signalling has been demonstrated to be involved in the modulation of reward processing and motivated behaviour (Rodriguez de Fonseca et al., 2005). There is ample evidence of the involvement of the eCB system in mechanisms of addiction (Maldonado et al., 2006; Self, 1998; Yamamoto et al., 2004) and addiction-related behaviours (Rodriguez de Fonseca et al., 1998; Rodriguez de Fonseca et al., 1999). In particular, endocannabinoids mediate the activity of dopaminergic neurons of the VTA, which consistently respond to drugs of abuse, and this response is thought to be related to the processing of the rewarding effects of drugs of abuse (Maldonado and Rodriguez de Fonseca, 2002). In humans, it has also been demonstrated to be involved in the regulation of dopamine release in the striatum (Bossong et al., 2009) and endocannabinoid antagonists have received considerable attention as potential pharmaceutical therapies for addiction (Beardsley and Thomas, 2005). Due to the ability of endocannabinoids to induce long term depression in the NAcc they could regulate the acquisition of habit formation and conditioned responses that is characteristic of drug addiction (Maldonado and Rodriguez de Fonseca, 2002; Maldonado et al., 2006).

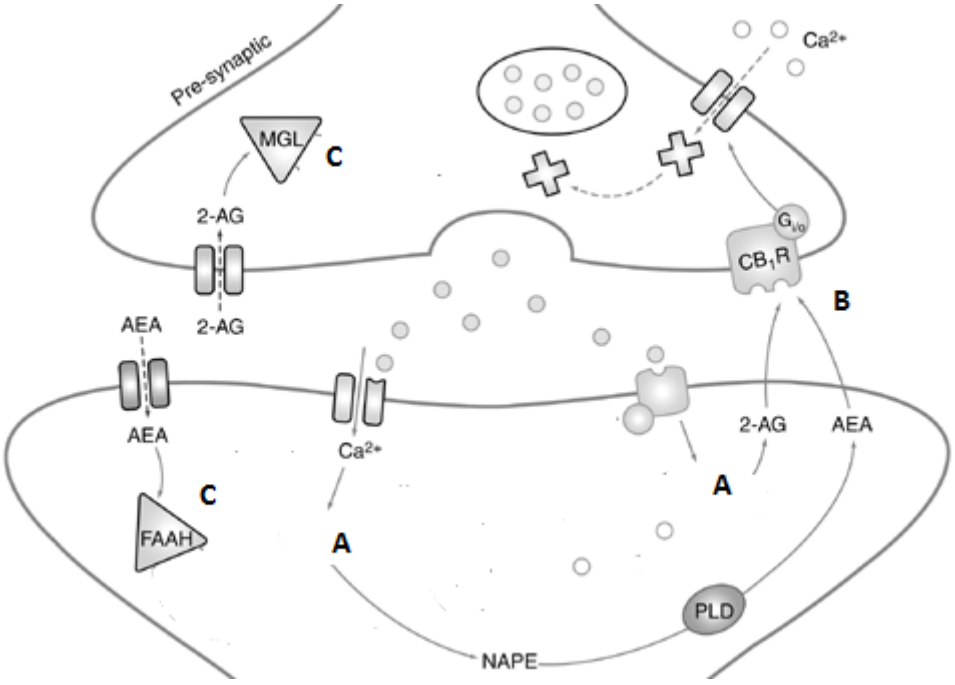


Figure 1.

Diagram of a cannabinergic synapse. (**A**) Synaptic transmission stimulates post-synaptic endocannabinoid (eCB) synthesis. (**B**) Retrograde eCBs hyperpolarize the presynaptic terminal, thus reducing further neurotransmitter release. (**C**) reuptake and degradation. Abbreviations: 2-arachidonoylglycerol (2-AG); anandamide (AEA); cannabinoid-1 receptor (CB1R); monoacylglycerol lipase (MGL); fatty acid amide hydrolase (FAAH). Figure adapted from: (Hosking and Zajicek, 2008)

Nicotine, Addiction and the endocannabinoid system

Addiction in general

Studies investigating addictive properties of drugs on behaviours have made use of a number of animal models that relate to drug-seeking behaviours. One of the most commonly used paradigms to model drug seeking and relapse phenomena is the self-administration extinction/reinstatement paradigm. The ability of certain drugs to induce drug seeking and self-administration behaviours in animals is thought to reflect their rewarding, motivational, and addictive properties. Once the animal has learnt to self-administer the drug, it is withheld, despite the continued responding of the animal in an attempt to self-administer the drug. Extinction is achieved once the animal no longer continues to respond, demonstrating a change in the motivation for drug seeking behaviour. Once this condition is achieved various factors that are thought to influence relapse to drug seeking can be experimentally investigated. Another paradigm that is commonly used is the conditioned place preference (CPP) paradigm. CPP is a phenomenon that is thought to reflect the rewarding and reinforcing effects of drugs and is an example of dopamine mediated incentive learning (Bardo and Bevins, 2000; Le Foll and Goldberg, 2005a). CPP is demonstrated by the preference of animals to locations which were previously associated with drug administration, and is used to model the effects of environment and the associated cues that are thought to facilitate drug seeking behaviours. A third animal paradigm used to assess the direct rewarding properties of drugs of abuse is the intracranial self-stimulation paradigm. In this method an electrode is inserted into the dopaminergic reward circuits of animals, with which they can directly stimulate this network to produce rewarding and pleasant effects. The rate of responding for self-stimulation reflects the baseline of dopaminergic reward functioning. In this manner the effects of various drugs of abuse on this reward system can be modelled through effects observed on the rate of self-stimulation in these animals.

A feature common to almost all addictive drugs is the involvement of the mesocorticolimbic dopaminergic reward system. The effects of drugs on the activity of the dopaminergic brain reward pathway is thought to be primarily responsible for their addictive properties (Koob, 1992a; Koob, 1992b; Wise, 1982; Wise, 2004). The regulation of dopamine transmission in this system is mediated by the activity of neuronal afferents arriving in the VTA. (Cheer et al., 2007; Lupica and Riegel, 2005; Maldonado et al., 2006; Zangen et al., 2006). Dopaminergic neurons of the VTA consistently respond to drugs of abuse, and this response is thought to be related to the processing of their rewarding effects (Maldonado and Rodriguez de Fonseca, 2002). Activation of the dopaminergic neurons of the VTA results in increased dopaminergic transmission in other areas of the dopaminergic mesocorticolimbic reward system through its projections to the NAcc, striatum and the prefrontal cortex (PFC). Additionally, blockade of dopamine transmission has been found to reduce the rewarding effects of psychostimulants (Koob, 1992a; Koob, 1992b). It has been reported that the dopaminergic neurons of the VTA are responsible for drug- induced relapse to drug seeking after abstinence (Kalivas and McFarland, 2003; Self, 1998; Shalev et al., 2002; Stewart, 2000; Wang et al., 2003), since damage to the cell bodies of dopamine neurons in the VTA abolishes drug-induced relapse (Leri et al., 2002; Wang et al., 2003).

Nicotine action and addiction

Nicotine and other drugs of abuse act similarly at the behavioural and neurobiological level (Picciotto, 1998). Animal studies investigating the rewarding and addictive properties of nicotine have demonstrated that it is able to elicit drug-seeking behaviour (Corrigall and Coen, 1989; Di Chiara, 2000). There is abundant evidence that it reinforces self-administration (Di Chiara, 2000; Stolerman and Shoaib, 1991), induces conditioned place preference (Le Foll and Goldberg, 2005a); (Di Chiara, 2000; Stolerman and Shoaib, 1991) and enhances reward from intracranial brain stimulation (Di Chiara, 2000). It has been observed that the same factors that are able to reinstate drug seeking behaviour have been found to also reinstate extinguished CPP for nicotine (Lu et al.,

2002; Mueller and Stewart, 2000; Sanchez and Sorg, 2001). In addition, cessation or abstinence produces a withdrawal syndrome (Stolerman and Jarvis, 1995) and reduces the reward function in rats as measured through behavioural effects on intracranial self-stimulation paradigms (Epping-Jordan et al., 1998). All of these effects are common to the action of addictive drugs of abuse in the brain's dopaminergic reward system. This is supported by observations that self-administration of nicotine in animals is reduced by administration of dopamine antagonists, or by lesions to the dopaminergic neurons of the NAcc (Corrigall and Coen, 1989; Corrigall et al., 1992; Corrigall et al., 1994; Corrigall, 1999).

Nicotine primarily exerts it effects on nicotinic acetylcholine receptors (nAChRs), which are formed by different possible combinations of five sub-units (Mansvelder and McGehee, 2002; Wonnacott et al., 1990; Wooltorton et al., 2003). Through its actions on these receptors, nicotine is able to modulate the activity of the mesocorticolimbic dopaminergic reward system (Pidoplichko et al., 2004; Pontieri et al., 1996). It has been observed that there is a prolonged firing of dopaminergic neurons in the VTA after nicotine administration (Pidoplichko et al., 2004). The increased concentration and prolonged dopamine signalling can be explained by examining the regulation of VTA neurons, which projects to the NAcc and striatum to regulate dopamine release. Due to the fact that the direct action of nicotine on nAChRs on VTA dopaminergic neurons is short lived, the prolonged regulation of transmitter release must be regulated through the indirect modulation of VTA neuron activity by glutamatergic and GABAergic afferents (Dani et al., 2000; Pidoplichko et al., 1997; Pidoplichko et al., 2004; Wooltorton et al., 2003). The differential effects of nicotine on these two neuronal populations can be accounted for by examining the differential expression of nAChRs on these neurons. It has been found that nAChRs containing the β-2 subunit are primarily responsible for regulating nicotinic activation of GABAergic afferents into the VTA whereas nAChRs containing the α-7 subunit mediate glutamatergic transmission (Pidoplichko et al., 2004). Subsequently, nAChRs on glutamatergic afferents do not significantly desensitise at the concentration of nicotine obtained from smoking, whereas the nAChRs on GABAergic neuronal terminals do desensitise after some exposure (Pidoplichko et al., 2004). Consequently, nicotine's action on nAChRs mediates the continued excitatory input, coupled with the reduced inhibitory transmission, which results in the enhancement of the activity of the VTA dopaminergic neurons.

There is also evidence from human imaging studies that the midbrain dopaminergic reward system is involved in the reward and addictive properties of nicotine (Martin-Solch et al., 2001; Wonnacott et al., 1990). Particularly strong evidence of nicotinic modulation of dopaminergic neurons in the ventral striatum comes from a PET study conducted by Brody and colleagues (2004). In this study the authors used ([^{11}C]raclopride bolus-plus-continuous-infusion) PET to measure nicotine induced dopaminergic release in a group of satiated smokers relative to a group of unsatiated smokers. It was found that in the group of smokers that had just smoked, there was a reduction in the binding potential of [^{11}C]raclopride in ventral striatal regions, especially in the left ventral caudate/NAcc and left ventral putamen, relative to the abstinent smokers. The reduction in binding potential of [^{11}C]raclopride is an indirect measure of dopamine release (Brody et al., 2004). The nicotine induced changes in dopaminergic transmission found in this study were comparable to other studies investigating the effects of other addictive drugs (Brody et al., 2004). Further evidence of the involvement of the dopaminergic reward system in nicotine addiction comes from another PET investigation conducted by Martin-Solch and colleagues (2001), which looked at the differences in brain activation associated with reward processing in smokers and non-smokers. In this study they found that non-smokers showed increased activation in the thalamus and striatal regions as well in areas of the reward system in response to reward stimuli. Conversely, smokers only showed increased activation in the areas of the reward system. It is thought that the reduced activation in the striatum of smokers in response to rewards could reflect changes in the mesocorticolimbic dopamine system associated with chronic exposure to nicotine (Martin-Solch et al., 2001). This idea is supported by the finding that there is a higher baseline of dopamine activity in the striatum of

smokers than non-smokers (Salokangas et al., 2000) independent of reward processing. Furthermore, in an fMRI study investigating the nicotine and cannabis induced long-term changes in brain activation in relation to reward anticipation, van Hell et al. (2010b) compared brain activation patterns between chronic cannabis users, smokers, and healthy controls during a reward anticipation task. With respect to the nicotine users and healthy control groups, it was found that long-term nicotine use resulted in attenuated reward anticipation activity in the NAcc in smokers relative to healthy controls. In another study, investigating changes in the functional connectivity of neuronal networks, Hong and colleagues (2009) showed that the strength of coherence between activity in the dorsal anterior cingulate cortex (dACC) and striatum was inversely related to the severity of nicotine addiction in abstinent smokers. Interestingly, acute nicotine administration did not modify this observed phenomenon.

Endocannabinoid involvement in addiction

The involvement of the endocannabinoid system in drug addiction has been well documented in a variety of animal models exploring this phenomenon. A mechanism for the involvement of the eCB system in a generalised role in addiction is supported by the fact that stimulation of CB1 receptors can induce reinstatement of extinguished self-administration behaviours in animals for almost all drugs of abuse (Shaham et al., 2003). CB1 stimulation with selective agonists potentiates the drug-induced reinstatement of drug seeking behaviour to opioids, cocaine, nicotine and alcohol (De Vries et al., 2001; Fattore et al., 2003; Fattore et al., 2007; Navarro et al., 2001). Moreover, it has also been documented that administration of CB1 antagonists decreases opioid (Navarro et al., 2001), Cocaine (Arnold, 2005), nicotine (Cohen et al., 2002) and alcohol (Colombo et al., 1998; Rodriguez de Fonseca et al., 1999) self administration in rats. A number of studies have examined the effect of administration of the CB1 antagonist rimonabant on drug-induced reinstatement of drug-seeking behaviour. These studies demonstrate that rimonabant is able to severely reduce or even abolish drug-seeking behaviour that is usually reinstated with a priming injection of the conditioned drug of abuse (Fattore et al., 2007). This effect has been demonstrated in cocaine (De Vries et al., 2001), heroin (De Vries et al., 2003; Fattore et al., 2003), and methamphetamine (Anggadiredja et al., 2004). Additionally, the reinforcing and motivational properties, and severity of withdrawal symptoms of several drugs of abuse were shown to be severely reduced in CB1 KO mice (Fattore et al., 2000; Ledent et al., 1999; Soria et al., 2005). The evidence of the eCB involvement in modulating drug seeking behaviour of almost all drugs of abuse points to a general role of the eCB system in modulating relapse phenomena.

The ample evidence in the literature of a dopamine-cannabinoid interaction in the mesocorticolimbic dopamine system in animals (Cheer et al., 2007; French et al., 1997; Gessa et al., 1998; Wu and French, 2000), suggests that CB1 may work to regulate the activation of dopaminergic transmission. Further support of this comes from the observation that the CB1 antagonist rimonabant decreases the dopamine enhancing effects of drugs (Cheer et al., 2003; Cheer et al., 2004; Cohen et al., 2002). In line with this, it has been observed that CB1 receptor agonists evoke intense bursts of firing in mesocorticolimbic dopaminergic neurons (French, 1997; French et al., 1997; Gardner and Vorel, 1998; Gardner, 2005; Wu and French, 2000). Furthermore, human imaging studies have also demonstrated the ability of cannabinoid agonists to induce dopaminergic transmission in the striatum (Bossong et al., 2009). It has been argued that although similar activity in the dopaminergic reward pathway is observed after administration of cannabinoid agonists and other drugs of abuse, the underlying mechanisms facilitating this pattern of activity differs (Lupica et al., 2004). Whereas addictive drugs directly stimulate the activity of dopaminergic neurons in the mesocorticolimbic reward pathway, the activity of dopaminergic neurons in response to cannabinoid agonists can be explained through their regulation of excitatory and inhibitory afferents to the VTA (Lupica et al., 2004). It has been demonstrated that endocannabinoids work as retrograde synaptic messengers in the VTA, and though this mechanism, regulate the activation or inhibition of dopaminergic neurons, by acting on glutamatergic and GABAergic synaptic terminals (Manzoni and Bockaert, 2001; Melis et

al., 2004a; Melis et al., 2004b). Due to their ability to regulate the activity of these afferents, endocannabinoids may therefore modulate the response of dopaminergic neurotransmission in response to other addictive drugs. Given the role of the dopamine reward system in modulating addiction, there is reason to believe that the role of the endocannabinoid system in modulating the addictive properties of various drugs of abuse is mediated through its interaction with the dopaminergic system.

Role of endocannabinoid system in nicotine addiction

The majority of studies investigating the effect of the endocannabinoid system in modulating nicotine addiction have focused on effects of the CB1 antagonist rimonabant. For example, Cohen and colleagues (2002) demonstrated that rimonabant was able to significantly reduce rate of responding related to drug self-administration and consequently the number of nicotine infusions in rats. It was also observed that this effect seemed to be related to the effect of rimonabant in blocking the nicotine-induced dopamine release in the NAcc. In a follow-up study, it was further demonstrated that rimonabant was able to reduce the maintenance of responding that was related to nicotine-associated cues (Cohen et al., 2005), after prolonged abstinence in rats. The same has been demonstrated with respect to the rimonabant mediated reduction in responding related to drug-induced reinstatement after abstinence (De Vries et al., 2005). Taken together these studies suggest that CB1 receptor activity is necessary for nicotine and nicotine-associated cues to serve as reinforcers of drug-seeking behaviour. In line with the previous findings, acute administration of rimonabant is able to inhibit the development and expression of nicotine induced CPP in rats (Forget et al., 2005; Le Foll and Goldberg, 2004). It is important to note however, that there are differences in the long and short-term effects of the cannabinoid system in modulating this effect. It seems that although activation of CB1 receptors is necessary for the induction of nicotine CPP, after longer time intervals, the same function seems to be assumed by processes independent of the eCB system (Forget et al., 2006).

In addition to the observations that both nicotine and cannabinoids both interact with the dopamine reward system, there is emerging evidence that this link is fundamental to the explanation of nicotine's addictive properties. Given that nicotine exerts its effect on the glutamatergic and GABAergic afferents to the VTA, and that the eCB system regulates the synaptic transmission of these synapses, it may not be surprising that the eCB system can modulate the effect of nicotine on the dopaminergic reward system. Additionally, it has been discussed that the nicotinic activation of dopaminergic transmission is modulated by the endocannabinoid system through interactions with nAChRs in the striatum (De Vries and Schoffelmeer, 2005; Le Foll and Goldberg, 2005b). In line with this, there is also emerging evidence of the role of the endocannabinoid system interacting with nicotine in the regulation of the brain's dopaminergic reward circuits in humans. In an fMRI investigation, van Hell et al., (2010a) demonstrated a clear interaction of the effects of nicotine and cannabinoids and associated long-term changes in the brain in relation to reward processing. Neuronal activation in response to reward related stimuli was examined in chronic cannabis users compared to a control group. In order to account of the possible effects of nicotine on reward processing in cannabis users, neuronal activation was also compared to a second control group consisting of (nicotine only) smokers. The task used to assess reward processing was a modified version of the monetary incentive delay task (Knutson et al., 2001) which has been previously demonstrated to reliably activate areas associated with reward processing (Kirsch et al., 2003; Knutson et al., 2001). This study demonstrated an attenuated neuronal response in the NAcc and caudate nucleus in relation to reward anticipation in chronic cannabis users when compared to healthy controls. Although the reduction in activation of the caudate nucleus could be attributed specifically to the effects of cannabis on these neuronal populations, the changes in the response of the NAcc to reward anticipation could also be attributed to nicotine, since no difference was observed in this area when comparing chronic cannabis users and the smoking control group.

Overall, these studies provide support for the existence of a role of the endocannabinoid system in nicotine addiction.

Since rimonabant can dose dependently block the nicotine-induced increase of dopamine in the NAcc (Cohen et al., 2002) it is likely that it works to reduce the reinforcing and rewarding effects of nicotine. In humans, findings of clinical trials investigating the potential of rimonabant as a therapeutic drug for the cessation of smoking further emphasize the role of the eCB system in addiction processes. In particular, rimonabant has received some considerable attention, and has been shown to prolong the maintenance of abstinence in quitting smokers (Le Foll et al., 2008). Perhaps due to the diverse functional roles that the eCB system is proposed to be involved in, these clinical trials were compromised by the induction of aversive side-effects such as increased levels of depression and anxiety (Le Foll et al., 2008). Despite this however, these trials did clearly show that modulation of the eCB system through the administration of endocannabinoid antagonists was able to significantly affect the rate of cessation success, and provide further support for the role of the endocannabinoid system in modulating mechanisms of nicotine dependence (Le Foll et al., 2008).

Nicotine, Attention and the endocannabinoid system

Attention does not refer to a single process in the brain but rather is comprised of a number of mechanisms that facilitate the filtering, selection, and processing of information. Given this overarching definition, it is not surprising that many aspects of cognition may be referred to as attentional processing, and which may be differentially recruited in response to different attentional demands. Adler et al, (2001) characterised attention as "the ability to concentrate on a specific stimulus over a period of time to the exclusion of extraneous stimuli." (pp. 266, Adler et al., 2001). This definition highlights and encompasses the important aspects and processes involved in attentional processing. Attention requires the ability to orient or focus on a particular stimulus or location in space as well as the ability to maintain that focus for a period of time. These two aspects are referred to as orienting and vigilance respectively. Depending on the task at hand, attentional processing may recruit or involve particular cognitive processes such as: the filtering and selection of stimulus information (i.e. defining what one is to attend to); engagement (or disengagement) of focus on that space/stimulus (i.e. orienting); and the effortful concentration to maintain focus on that stimulus or space (i.e. vigilance). Furthermore, it should be noted that attention can be driven by bottom-up stimulus processing or top-down cognitive processing. That is to say, one can wilfully attend to something that they choose to (top-down) but also that sometimes when a sufficiently salient stimulus is presented to us it can 'break in' to our attentional processes and 'grab our attention'. The ability for salient stimuli to 'grab' our attention is sometimes referred to as the alerting component of attention. Whereas the bottom-up attentional modulation is driven by stimulus processing and filtering, top-down attentional modulation is modulated by more executive functions. In an attempt to study the different mechanisms and processes involved in attention, experimental models have categorised attention into different subtypes. For example, selective or sustained attention generally refers to the ability to selectively attend or focus on a specific stimulus or visual spatial location, and to maintain focus on that stimulus or location. Studies investigating divided attention on the other hand, require participants to divide their attention. That is to say they may be required to attend to a particular stimulus or location in space while at the same time monitoring for changes in another location or stimulus.

One of the most widely used paradigms to study sustained attention is the Continuous Performance Task (CPT). The CPT typically requires attention to be directed to a continuous stream of stimuli in order to monitor for the presentation of a particular target stimulus which prompts a response to be given (Keilp et al., 1997). One particular variant of this paradigm is the CPT-identical pairs (CPT-IP) version. In this instance, rather than a specific stimulus being the target, subjects are required to monitor the stream of presented stimuli and respond whenever the same stimulus is presented twice in a row. The CPT primarily measures orienting and vigilance since one is required to orient towards the stimulus presentation and maintain vigilance while monitoring for a response cue. Functional neuroimaging studies have revealed a number of brain regions that are thought to be involved in various aspects of attentional processing. In general, attentional tasks have been found to activate anterior structures that are involved in modulating attentional processing and more posterior structure that are involved in sensory integration and stimulus processing. For example, simply attending to a particular location in space, also during a CPT, is strongly associated with activation of the frontal cortex (Lewin et al., 1996). Experiments using CPTs have also consistently revealed activation of the frontal and prefrontal cortices. In particular, CPTs result in increased activation of the anterior cingulate (Benedict et al., 1998; Hager et al., 1998; Pugh et al., 1996), the medial frontal cortex (Benedict et al., 1998), the inferior frontal gyrus (Pugh et al., 1996) and the dorsolateral prefrontal cortex (Hager et al., 1998; Pugh et al., 1996). Additionally, the anterior insula has also been shown to be consistently activated by CPTs. More posterior brain regions that are implicated in attention include temporoparietal regions (Benedict et al., 1998; Hager et al., 1998; Pugh et al., 1996), including the fusiform gyrus and inferior parietal lobule, and structures of the striatum and basal ganglia such as: the caudate; claustrum; and thalamus (Hager et al., 1998).

Given the wide range of different brain regions involved, it has been proposed that different areas, or networks of areas, are involved in different aspects of attentional processing and are therefore differentially recruited depending on the task at hand. In particular, as part of the default mode network (Buckner et al., 2008; Mason et al., 2007; Raichle et al., 2001), there are two frontoparietal neuronal networks that are thought to be specifically associated with attentional processing – the ventral attention network and the dorsal attention network. The dorsal attentional network includes regions of the medial and lateral frontal cortices, and also in and around the intraparietal sulcus and superior parietal lobule (Corbetta et al., 2000; Corbetta et al., 2005; Kastner et al., 1999). The ventral attentional network consists of areas including the temporoparietal junction and the ventral frontal cortex (Corbetta and Shulman, 2002).Whereas the dorsal attention network is bilateral, the ventral attentional network is lateralised mainly to the right hemisphere of the brain. It is thought that the dorsal attention network is involved in more top-down attentional processes, while the ventral attentional network is more involved in disengagement, stimulus filtering and processing (Buckner et al., 2008; Corbetta and Shulman, 2002; Mason et al., 2007; Raichle et al., 2001).

Some of the regions involved in attentional processing outlined above have also been shown to involve dopaminergic transmission, including areas of the striatum, NAcc and PFC (Nieoullon, 2002). Further evidence of the involvement of dopamine in attention control comes from investigations into psychiatric disorders involving attentional deficits. In particular, attention has been reported to be affected in patients with ADHD, Schizophrenia and Parkinson's disease (Nieoullon, 2002), which are all thought to involve abnormalities in dopaminergic transmission (Solanto, 1998). Additional support for the role of dopamine in attentional modulation is also found in animal studies that have shown that lesions to the dopaminergic neurons of rats and primates results in particular cognitive deficits, including significant changes in attentional processes (Nieoullon, 2002). In addition to a role for dopaminergic transmission in regulating attention, the cholinergic system (on which nicotine primarily exerts it effects) has also been heavily implicated in the regulation of various aspects of attention (Phillips et al., 2000; Stewart et al., 2001; Witte et al., 1997). An ascending cholinergic system (arising from the reticular formation and the brainstem) is thought to facilitate the diffuse activation of cortical areas in relation to attentional and vigilance control (Posner, 1980). Given the evidence of nicotinic modulation of cholinergic neurons and the interaction of the eCB system and nicotine in the regulation of the dopaminergic transmission, it would be interesting to examine if the eCB system and nicotine interact in relation to attentional control. This section of the thesis will explore the effects of nicotine on attention and the possible role of the endocannabinoid system in mediating these effects.

Nicotine and attention

Through its actions on the cholinergic and dopaminergic systems, nicotine has been hypothesised to modulate attentional networks (Stewart et al., 2001; Witte et al., 1997). It has been previously demonstrated that acetylcholine is able to facilitate aspects of attentive behaviours, including sustained and selective attention (Muir et al., 1994; Phillips et al., 2000; Witte et al., 1997). Studies investigating the effects of acute nicotine administration on attention in animals have demonstrated that nicotine is able to selectively enhance particular aspects of attention. In particular, nicotine has been shown to affect orienting aspects of attention, but not alerting aspects (Stewart et al., 2001; Witte et al., 1997; Phillips et al., 2001). Using a cued target selection paradigm, Stewart et al. (2001) demonstrated that in rats, nicotine administration was able to facilitate attentional orienting through reduction of reaction times to target detection in invalidly cued trials. This effect is thought to result from a facilitation of disengagement and reorientation mechanisms of attentional control. Further evidence of a specific nicotinic mechanism in the regulation of this orienting aspect of attention comes from the observation that this effect was abolished with administration of the nicotinic antagonist mecamylamine in a dose dependent manner (Stewart et al., 2001). In line with the previous observations of the selective nature of nicotinic facilitation of attentional processes, neither

nicotine nor mecamylamine were found to have an effect on alerting scores in this study (Stewart et al., 2001). The findings from this study confirm and support observations from other studies that demonstrated similar effects of nicotinic modulation of attention in rats (Phillips et al., 2000) and monkeys (Witte et al., 1997).

In humans, it has also been found that acute nicotine administration is able to improve various cognitive functions (Kumari et al., 2003) including sustained attention in non-smokers as measured by continuous performance tests (Levin et al., 1998; Levin et al., 2001). In line with animal research, nicotine has been found to selectively affect the orienting but not alerting aspects of attention in humans (Murphy and Klein, 1998). The eye-blink startle response is a reflex that is slow to habituate and is known to be sensitive to attentional modulation in both humans and rats (Baschnagel and Hawk, 2008). A reduction in the magnitude of this eye-blink response is observed if a non-startling stimulus is presented 60-500ms before the startle stimulus. This effect is known as short-lead pre-pulse inhibition (PPI), and is thought to reflect an automatic stimulus gating process. Conversely, a long lead pre-pulse facilitation (PPF) effect is also observed if the pre-pulse stimulus is more than 800ms before the startle stimulus, resulting in a larger eye-blink response. When the pre-pulse stimulus is the focus of attention, both the PPI and PPF effects are enhanced (Filion et al., 1993; Hawk et al., 2002; Jennings et al., 1996), demonstrating the sensitivity of these effects to attention. Nicotine administration has been demonstrated to enhance PPI in rats (Acri et al., 1991) human smokers (Duncan et al., 2001; Kumari et al., 1996) and non-smokers (Kumari et al., 1997; Postma et al., 2006). Expanding on a study conducted by Rissling (2007), which demonstrated that short lead PPI was disrupted in abstinent smokers compared to satiated smokers and non-smokers conditions, Baschnagel & Hawk (2008) conducted a study investigating the effects of acute nicotine administration on the attentional modulation of the PPI and PPF effects in non-smokers. This study found that nicotine increased short lead PPI compared to placebo, but also more importantly, that a smaller effect of attentional modulation of the PPI in the placebo condition was associated with a larger increase in attentional modulation of the PPI during the nicotine condition. With respect to long-lead PPF, a greater effect was observed when the stimulus was attended to, compared to when ignored, but no modulation of this was observed by nicotine administration. Another study, conducted by Thiel and Fink (2008) investigated the effects of nicotine on voluntary top-down processes of attention and associated brain activation using fMRI. They used a spatial location target cuing paradigm to investigate the influence of nicotine on disengaging and reorienting attention. This paradigm uses the fact that our ability to discriminate visual stimuli is enhanced when we voluntarily direct our attention to the cued location of the target stimulus, and that misleading information on the location, delays target detection. The difference between reaction times to validly cued targets versus invalidly cued targets is known as the validity effect, and this is thought to be an indicator of the costs of disengaging and redirecting attention (Posner, 1980). Previous studies have shown that nicotine is able to reduce the reaction times to unattended stimuli, resulting in a reduction of the validity effect (Murphy and Klein, 1998; Phillips et al., 2000; Witte et al., 1997). It is possible that the reduction in the validity effect observed is due to a facilitated disengagement of attention from the cued location or that there is a reduced reliance on the cue information to begin with. The findings of this study demonstrated a validity effect as expected, confirming the attentional modulation of target detection. Interestingly, a reduction in the validity effect was observed under nicotine relative to placebo conditions. This effect however was initially insignificant, but it was found that 4 of the 13 participants did not show a validity effect under placebo conditions. When these individuals were removed from the analysis, the reduction of the validity effect under nicotine administration was revealed to be significant. The reduction in the validity effect was due to a reduction in the reaction times to invalidly cued trials, and no difference was observed in the validly cued trials. When comparing placebo and nicotine conditions, cue validity and the modulation of cue validity by nicotine was found to be related to brain activation differences in the right middle temporal gyrus, the left inferior frontal gyrus, and the right angular gyrus. Additionally, a reduced activation of the right inferior parietal cortex to invalidly cued trials was observed under nicotine relative to placebo

conditions. Increased neural activity to invalid versus valid trials was observed in frontoparietal regions, a finding that is supported by previous research (Corbetta et al., 2000; Thiel et al., 2004; Vossel et al., 2006).

The study by Rissling et al., 2007 demonstrated that nicotine withdrawal in smokers reduced the effects of the PPI on eye-blink startle responses relative to non-smokers and satiated smokers. In line with this, the study of Baschnagel & Hawk (2008)demonstrated a facilitative effect of acute nicotine administration on the attentional modulation of the short lead PPI relative to placebo, whereas no effect of nicotine was observed with respect to the attentional modulation of the long lead PPF effect on the magnitude of the eye-blink startle response. These results suggest that nicotine is only able to enhance early automatic attentional stimulus filtering and gating. In support of this, the study by Thiel and Fink (2008)revealed that there was no increase in reaction times to validly cued trials in nicotine relative to placebo conditions, whereas a reduction in reaction times to invalidly cued trials was observed. These results are in line with the observations of a nicotinic mediated reduction in invalidly cued trials with rats, as demonstrated by the study of Stewart at al., (2001). This suggests that nicotine facilitates disengagement and reorientation processes rather than reducing the use of cue information for orienting attention. Enhanced stimulus filtering would facilitate stimulus detection and selection. Earlier stimulus detection could therefore result in an earlier realisation that the cue information was misleading in invalidly cued trials, and consequently facilitate orientation to the real target location, resulting in the observed reduction in the reaction times to invalidly cued trials but not validly cued trials. Additionally, the increased activation in the inferior frontal gyrus and reduced activation in the inferior parietal cortex observed under nicotine relative to placebo administration is in the ventral attentional network, which is thought to be involved in attentional processes of stimulus filtering and selection. Another important conclusion that can be drawn from these studies is that the effect of nicotine on attention is dependent on the initial baseline of attention observed under placebo conditions. Baschnagel & Hawk (2008) demonstrated that the effect of nicotine on the attentional modification of the PPI effect was dependent on (and inversely related to) the extent of attentional modification during placebo. The study by Thiel and Fink (2008)showed that the effect of nicotine modulation in reducing the validity effect was only observed in individuals who had an initially larger validity effect in the placebo condition. These observations provide further support to previous findings. Newhouse et al., (2004) demonstrated that the beneficial effects of nicotine on attention were inversely related to baseline attentional functioning. Additionally, Poltavski & Petros (2006) also showed that nicotine improved sustained attention in a continuous performance task in non-smokers, but only in those who had a low level of self-reported attention. Taken together these finding suggest that individuals who are less able to filter stimulus processing with attention are the ones that benefit most from the nicotinic enhancement of the attentional modulation of stimulus gating. Overall, the reported differential effects of nicotine, dependent on the initial baseline of attentional control, could once again indicate that individuals with particular attentional deficits are more likely to smoke due to the enhancing effects of nicotine on attention, and that the individuals that do not have these deficits do not benefit from the cognitive enhancement of nicotine and so are less attracted to smoking

Although it is important to tease apart the influences of withdrawal relief and true facilitative effects of nicotine in smokers in order to understand the effects of nicotine on attention, the withdrawal symptoms themselves are informative with respect to the long-term influence of nicotine on cognition. For example, performance on attentional and other cognitive tests has been found to be impaired within a few hours of abstinence in smokers (Leventhal et al., 2007; Snyder et al., 1989). The strongest impairment in cognitive functioning under nicotine withdrawal has been reported in sustained attention and working memory tasks (Hendricks et al., 2006). In smokers, abstinence from nicotine can be viewed as a perturbation of their 'normal' brain function, which has adapted to the continued presence of nicotine (since smokers usually consistently self-administer nicotine). Since, abstinence produces attentional deficits it seems apparent that nicotine must exert its effects on the

neuronal populations involved in this attentional control, which are consequently perturbed by nicotine abstinence. However, these conclusions must necessarily be tentative due to the possible confounding factors that arise from the chronic administration of nicotine. It may well be possible that the chronic administration of nicotine differs from the acute administration of nicotine in non-smokers, due to brain changes that have occurred in the development of dependence to nicotine. In support of the finding that nicotine plays a role in the attentional system of smokers in withdrawal relief, it has been observed that nicotine generally increases sustained, divided, and focused attention among abstinent smokers (Baschnagel and Hawk, 2008).

Additional support for the role of nicotine in modulating attentional systems can be found in literature examining the relationship between smoking and various psychiatric disorders involving attentional deficits. A number of studies have described a strong relationship between cognitive deficits in attention and smoking (Kumari and Postma, 2005; Newhouse et al., 2004; Potter and Newhouse, 2004). For example high rates of smoking have been reported in individuals with certain attentional related cognitive disorders (Kumari and Postma, 2005; Mihailescu and Drucker-Colin, 2000a; Mihailescu and Drucker-Colin, 2000b) such as attention-deficit-hyperactivity-disorder (ADHD) and schizophrenia. These investigations suggest that individuals with these disorders are more likely to benefit from the possible facilitative effects of nicotine on attention and therefore smoke to alleviate their attentional deficits. With respect to ADHD in particular, a recent study conducted by Pomerleau et al. (2000) demonstrated that adults with ADHD, compared to the general population, have higher rates of smoking (40% compared to 26%) and reduced success in quitting (29% compared to 48.5%). This seems to be quite a robust finding and is supported by findings from a number of different studies (Barkley et al., 1990; Gehricke et al., 2007). A number of studies have demonstrated that acute nicotine administration is able to improve concentration and reaction times in attentional tasks in both smokers and non-smokers with ADHD (Conners et al., 1996; Levin et al., 1996). Additionally, whereas acute nicotine administration reduced the severity of ADHD clinical symptoms and self reported depression, chronic nicotine administration did not influence the severity of clinical symptoms, but did exhibit antidepressant benefits (Levin et al., 2001). This difference may reflect the changes in brain responsiveness to nicotine in the development of addiction. It is therefore possible that individuals with ADHD smoke initially to alleviate attentional deficits; however, as nicotine dependence develops, these benefits may be reduced and become secondary to, withdrawal alleviation which then continues to drive smoking behaviour.

The endocannabinoid system and attention

Given the findings that nicotine modulates attentional processes and that the eCB system has been implicated as being important to a number of aspects of nicotinic effects, it is also quite possible that the eCB system could modulate the effects of nicotine on attention. This seems even more likely when one considers the fact that dopaminergic transmission is implicated in the regulation of attentional processes and that both nicotine and endocannabinoids have been shown to be able to modulate dopaminergic transmission in the midbrain reward system. Although attention regulation may involve different neuronal populations than those in which these interactions have been demonstrated, the fact that these interactions have been identified in these areas raises the possibility that they may also interact in other neuronal populations as well. As of yet, there have not been many studies conducted specifically examining the effects of the eCB system in modulating the attentional effects of nicotine. However, tentative implications can be extrapolated from examining independent effects of cannabinoids and nicotine on attention. For example, eCB mechanisms have been implicated in processes relating to working memory, which also involves attentional processes. In support of this, the high densities of the CB1 receptors observed in the basal ganglia, cerebral cortex and hippocampus could be taken as an indication that the cannabinoid system is involved in attentional and memory processes (Roser et al., 2008).

In a study investigating the effects of the cannabinoid system in mediating visuospatial attention processes in rats, Arguello and Jentsch (2004) investigated the differential effect of CB agonists and antagonists on a lateralized reaction time task in rats. This task is thought to reflect processes of visual divided and sustained attention (Arguello and Jentsch, 2004). The results of this investigation demonstrated that administration of a CB1 agonist resulted in impaired performance on the visuospatial attention task in a dose dependent manner. Whereas, the CB1 receptor antagonist rimonabant did not result in any observable effects in performance when administered alone, it was able to effectively block the impairment in performance when co-administered with the CB1 receptor agonist. Taken together, these results provide convincing support for the role of the eCB system in modulating attentional processes through the actions of the CB1 receptor.

In a study investigating the effects of acute THC administration on the P300 evoked response potential (ERP), Roser et al., (2008) demonstrated a modulation of this evoked response with cannabinoid administration. The P300 ERP is thought to be a direct reflection of attentional resource allocation and active working memory (Polich, 1991). The results of this study demonstrated a reduction in the amplitude of the P300 ERP associated with acute administration of THC. A reduced amplitude in the P300 response reflects deficient attentional resource allocation and working memory systems, and so this study demonstrated a reduction in attentional processing associated with endocannabinoid agonists. The results of this study are in line with previous findings that have reported cognitive impairments in attention and memory during acute THC administration (Solowij, 1998). In a study investigating the acute effects of THC administration on a divided attention signal detection task in frequent cannabis users and non users, Marks and MacAvoy, (1989) demonstrated that acute THC administration impaired performance in both users and non users. The divided attention signal detection task required participants to monitor two possible sources of a signal, and respond whenever a signal was presented from either source. THC administration resulted in longer reaction times and more errors in signal detection in both groups relative to placebo. The effect of THC on performance reduction however, was stronger in the non-users group relative to the cannabis users group, perhaps reflecting some of the adaptive changes in the brain that result from frequent cannabis use. These observations are supported by findings from another study investigating differences in cognitive performance in a variety of tasks between occasional cannabis users and frequent cannabis users (Ramaekers et al., 2009). Acute THC administration was found to result in reduced performance on a divided attention task only in the occasional cannabis users group and not the frequent users group. Overall, the above studies highlight some of the effects of acute THC administration on performance in attention-dependent tasks. Although THC administration results in differences in performance to attention tasks in both users and naive subjects, these studies suggest that the specific effects of THC administration on performance may differ between these groups. A PET investigation using [^{15}oxygen]-labelled water ([^{15}O]-H_2O), was conducted by O'Leary et al., (2002) in order to investigate whether acute THC administration resulted in differences in regional cerebral blood flow (rCBF) during a auditory attention task, in which subjects were required to respond whenever a target tone was presented. Relative to the placebo condition, THC administration resulted in increased rCBF in the orbital and medial frontal lobes, the insula, and anterior cingulate. Reduced rCBF was also observed in the parietal and frontal lobes as well as the thalamus and was "localised to brain regions that mediate sensory processing and attention." (pp. 811, O'Leary et al., 2002). This study supports the previous findings that performance on attention tasks is affected by THC administration, as demonstrated by altered brain patterns in regions involved in attentional processing under THC administration relative to placebo.

In addition to the acute effects of the eCB system in attentional control, further evidence of the involvement of the eCB system in mechanisms underlying attention come from the observations that long-term administration of THC in healthy volunteers induces cognitive impairments (Solowij et al., 1991). In particular, interest has focussed on long-term changes in memory, learning, executive functioning and attention, associated with chronic cannabis use (Block et al., 2002; Eldreth et al.,

2004; Jager et al., 2007; Solowij et al., 2002). Additionally, an attenuation of the P300 amplitude has been reported in long-term cannabis users when compared to healthy controls (Solowij et al., 1991). Abdullaev et al., (2010) conducted an fMRI study investigating differences in brain activation patterns between chronic cannabis user adolescents and non-user adolescents during two attentional tasks. The two attention tasks were designed so that performance with respect to different aspects of attention (alerting, orienting and executive control) could be delineated from one another (See: Abdullaev et al., 2010). The authors reported that chronic cannabis users exhibited a poorer performance relative to non-users in tasks requiring executive attentional control but not in tasks reliant on orienting or alerting aspects of attention. In line with the differences in performance, activation of brain areas was found to be different between users and non-users only in tasks requiring executive attentional control, with chronic cannabis users exhibiting stronger activation in the right-PFC (Abdullaev et al., 2010). Together with the results of Roser et al., (2008), these observations suggest that the acute effects of cannabinoids on the modification of attentional processes is reflected in long-term changes of the neuronal populations regulating these processes. In general, previous studies support the idea of impairment in attention and working memory systems through the action of CB1 agonists on prefrontal and hippocampal neuronal populations (Ranganathan and D'Souza, 2006; Solowij, 1998). Although, no studies have been conducted investigating the specific involvement of the eCB system in the modulation of the effects of nicotine on attention, these findings indicate that it is involved in processes of attentional control in general. Given the fact that nicotine is also able to modulate attentional processes, there is a possibility for an interaction between nicotine and the eCB system in the regulation of attentional control.

Discussion

In the preceding chapters we have provided evidence from experiments investigating the possible links between nicotine and the endocannabinoid system with respect to addiction, and attention. In the following section we will review these findings and discuss the possible links between attention and nicotine addiction, and how the endocannabinoid system may be implicated in this, by drawing on the findings discussed. We will then go on to introduce some experiments carried out at the University Medical Centre Utrecht, and discuss the implications of the conclusions drawn from this thesis for these experiments.

The endocannabinoid system has been found to be widely expressed in a number of different brain regions and has been shown to operate as a retrograde synaptic messenger system that regulates the synaptic communication of a variety of different neurotransmitter systems. The diffuse expression, and the ability to modulate the strength of synaptic connections, places the endocannabinoid system in an ideal position to regulate a variety of different cognitive functions. In particular we have provided evidence for the role of the eCB system in modulating the activation of the mesocorticolimbic dopaminergic reward pathways of the brain through its actions on the excitatory and inhibitory afferents of the VTA. The ability of the eCB system to modulate the activity of this reward system is thought to be fundamental to the explanation of its interactive effects with the actions of almost all drugs of abuse. Consequently, given the hypothesised importance of the dopaminergic reward pathway in mechanisms of addiction, the ability of the eCB system to modulate the activation of this pathway in response to drugs is thought to be of vital importance to its potential role as a therapeutic target for the treatment of addiction. In this thesis we have focused primarily on the role of the eCB system in modulating nicotinic effects and the consequences of this interaction on nicotine addiction. Nicotine has been shown to exert its effects on nicotinic acetylcholine receptors and influence the excitatory and inhibitory afferents to the VTA and in this manner is able to directly modulate the activity of the dopamine reward system. Given the fact the both nicotine and the eCB system affect the activity of the same neuronal afferents to the VTA it is not surprising that an interaction would be observed with respect to their effects on the dopaminergic reward pathway.

Convincing evidence of nicotine's addictive potential is provided by animal studies that show that nicotine is able to induce drug seeking behaviour and self-administration, as well as induce CPP and enhances the reward function of the dopaminergic system as measured through intracranial self-stimulation experiments. Evidence for the fundamental role of the dopaminergic system in maintaining nicotine addiction stems from the observation that lesions to the NAcc are able to reduce or inhibit the acquisition or expression of self-administration behaviours of nicotine in rats. The findings of these studies have been confirmed from human imaging data that have shown that chronic nicotine administration alters the activation patterns of brain regions involved in processing reward and thereby implicating the mesocorticolimbic dopaminergic pathway. In particular altered activation in reward processing has been observed in the striatum in smokers compared to non-smokers, and this finding is supported by the observation that under normal conditions there is a greater level of dopamine transmission in the striatum of smoker relative to non-smokers. The effect of nicotine on the activity of the dopaminergic mesocorticolimbic reward system is mediated through its effects on the excitatory and inhibitory afferents to the VTA. Given that the eCB system works as a retrograde synaptic messenger in these neurons, it is ideally suited to modulate or override the effects that nicotine exerts on VTA dopaminergic neurons, consequently affecting the rewarding and reinforcing properties of nicotine.

Although cannabinoids have been shown to elicit activation of the dopaminergic reward system in a similar pattern to other drugs of abuse, the mechanisms by which this effect is achieved is proposed to be different. The ability for cannabinoid agonists to increase the activity of these neurons is a

possible explanation for the addictive potential of natural cannabinoid agonists such as THC. However, the difference in the proposed mechanisms by which cannabinoids and other drugs of abuse influence the activity of dopaminergic neurons is thought to be fundamental to the mechanism by with the eCB system can modulate the effects of other drugs on the dopaminergic reward pathway. Evidence for the involvement of the eCB system in modulating the effects of other drugs of abuse comes from animal studies demonstrating that eCB antagonists are able to inhibit or abolish drug seeking behaviours as measured through self-administration paradigms. Additionally, it has been demonstrated that CB1 KO mice do not develop drug seeking behaviours or withdrawal symptoms from various drugs. Taken together, these findings support the idea for a generalised role of the endocannabinoid system in addiction processes. There is also convincing evidence in the literature for a specific role of the eCB system in nicotine addiction as demonstrated by animal studies that show that cannabinoid antagonists such as rimonabant are able to reduce the rate of responding in for self-administration of nicotine. This observation is thought to be mediated through the effects of rimonabant on blocking the nicotine mediated dopamine release in the NAcc. Additionally, further evidence for the potential of rimonabant to modulate nicotine mediated effects is demonstrated by the fact that rimonabant can abolish drug-induced reinstatement of drug seeking behaviour. This is supported by findings that show that the CB1 receptor is necessary for nicotine and nicotine-associated cues to reinforce drug seeking behaviours. In accordance with the previous observations that nicotine is able to mediate changes in the activity of areas of the brain related to reward processing, and that the eCB system can modulate the activity of this system, clinical trials for the effectiveness of rimonabant as a therapeutic drug for the treatment of nicotine addiction have shown that it is able to prolong abstinence in quitting smokers, and increases the rate of success for smoking cessation. Taken together these results provide strong indications that, through the modulation of nicotinic effects on the dopaminergic reward pathway, the eCB system is able to reduce the rewarding and reinforcing properties of nicotine and therefore affect the motivational salience of nicotine.

With respect to attention the following observations have been discussed in this thesis. Acetylcholine has been shown to facilitate sustained and divided attention and given that nicotine exerts its effects on nAChRs there is emerging evidence that nicotine is able to modulate specific mechanisms involved in attentional processing. Dopaminergic transmission has also been shown to be important in attentional processing, and nicotinic effects on dopamine transmission may also account for its effects on attentional processes. In particular nicotine has been shown to enhance the orienting aspects of attention in both animal studies and human imaging experiments. The alerting aspects of attention however do not show this modulation. Orienting aspects of attention can be facilitated if stimulus processing and selection is enhanced, and determines where and what we attend to. Enhanced stimulus filtering and selection would facilitate (dis)engagement processes of attention, which would result in facilitated orienting of attention. Given the fact that nicotine is able to modulate this aspect of attention, it is possible that this modulation is responsible for the fact that smokers orientate their attention to nicotine associated cues more, and maintain focus on these cues for longer than non-smokers. It is also possible that this modulation is also responsible for the ability of nicotine associated cues to elicit craving and motivation for nicotine seeking behaviour, as has been demonstrated in both animal and human studies. Additional evidence for the role of nicotine in modulating attention is provided from observations that the withdrawal symptoms of nicotine involve impairments in attention, and the co-morbidity of smoking behaviour that is observed in psychiatric disorders that are associated in particular deficits in attention. Nicotine administration has been shown to result in a reduced activation of areas of the ventral attentional network, which is mainly implicated in stimulus filtering and orientation processes of attentional control. Further support for the idea of a relationship between attention and nicotine addiction is provided by observations that the modulation of attention by acute nicotine administration is dependent on the initial baseline of attentional modulation observed in individuals. The extent to which nicotine is able to modulate attention may be greatly enhanced in individuals that show less attentional modulation

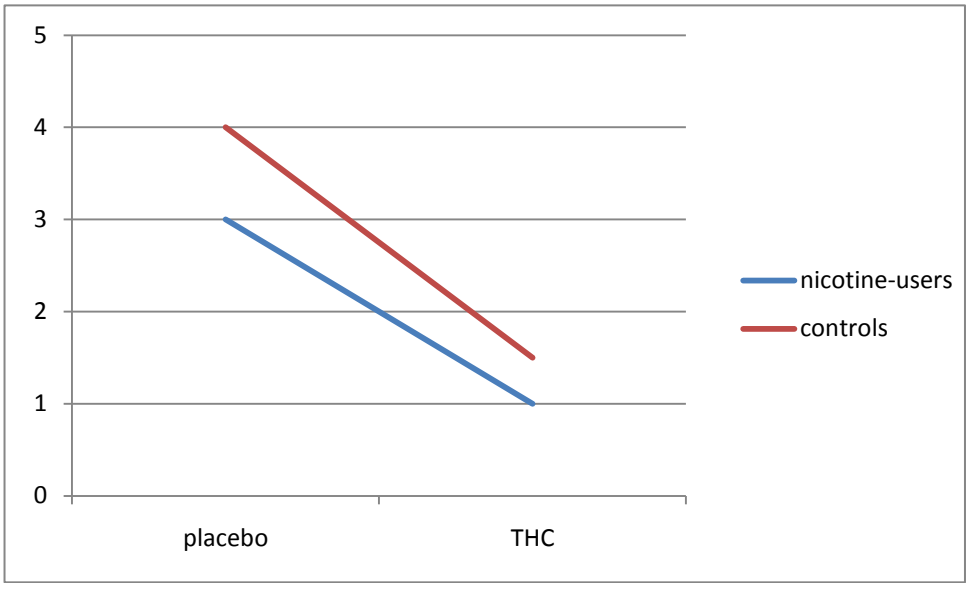
in cognitive tasks that involve attentive processes. It is also possible that individuals with lower attentional baselines of attention, benefit most from the facilitative effects of nicotine, and so are more at risk to nicotine addiction. In line with this there are observations that the populations of smokers and non-smokers differ on a variety of dimensions including personality traits and genetic factors. It is therefore possible that attentional processes may also be reflected in these differences. Further indirect support for a possible relation between attention and nicotine addiction comes from the observation of elevated smoking rates, and greater facilitative effects of nicotine on attention, in patients with psychiatric disorders involving attentional deficits. Although currently the role of the eCB system in this relationship is not yet clear, the evidence provided indicates that the endocannabinoid system may provide a link for the relationship between attention and nicotine addiction

The eCB system has also received some attention with respect to its ability to modulate attentional processing. In particular interest in this area has been driven by investigations into the possible effects of (chronic) cannabis use on attention. Evidence from animal studies suggest that CB1 agonists, such as THC, impair performance in sustained and divided attention tasks. Further evidence of the particular involvement of the eCB system in this effect is provided by the fact that rimonabant is able to block the effects of these agonists on attention. Human studies also confirm this observation since the P300 response, which is thought to reflect working memory and attentional resource allocation, is impaired with acute THC administration and after long-term cannabis use. Currently, there have not been many studies investigating a direct relationship between the effects of nicotine and the eCB system with respect to their effects on attention. However, the studies reviewed in this thesis provide impetus for the idea of a connection between the two. For example, nicotine has been shown to primarily affect orienting aspects of attention while THC has been shown to attenuate the P300 response, which is thought to be a reflection of resource allocation of the attentional system. Preliminary findings from a PET auditory attention task, indicates that acute THC administration has been shown to result in a decreased activation of areas involved in sensory processing and attentional control. This study however, only tested 5 subjects and so is not entirely conclusive.

Interestingly, studies investigating the long-term effects of THC on attention have reported that chronic exposure results in impaired executive attentional control, but not orienting or alerting aspects. The difference in the aspects of attention that are affected by acute administration and long-term exposure may reflect some of the adaptive brain changes that occur from the long-term effects of THC. Although initially THC may affect orienting and stimulus filtering aspects of attention, chronic exposure may allow for the brain to compensate for the impairment, and consequently improve this aspect of attentional processing while still under the effects of THC. This compensation may however require a greater load to be placed on the voluntary executive control of attention, resulting in the observed impairment after long term exposure. This is supported by the observation that despite similar performance on attentional tasks, there is increased activation in the right-PFC of chronic cannabis users relative to non-users. Given the role of the eCB system in modulating the effects of nicotine on dopaminergic transmission, and that there is evidence of an involvement of the dopamine in attentional processes, it is plausible that the eCB system may also work to modulate nicotine's effects on attention.

We will now briefly discuss an experiment conducted in the Rudolf Magnus Institute of the University Medical Centre Utrecht. The experiment used a CPT-IP paradigm to measure attentional functioning in ten heavy nicotine users and thirteen group-matched controls after THC administration, relative to a placebo controlled condition. THC or placebo administration tests were conducted on different days. After administration subjects performed the CPT-IP task while in an MRI machine, and performance and brain activation patterns were recorded. Given the findings discussed in this thesis I would hypothesise the following results from these experiments.

The control group and condition (non-nicotine users, placebo administration) will provide a baseline from which the effects of chronic nicotine use and THC administration effects on performance and brain activation will be measured against. I would expect the areas of the brain activated as a result of the CPT-IP task would include areas of voluntary attentional control, such as the (DL)PFC, anterior cingulate and thalamic regions. Additionally, areas of both the dorsal and ventral attention networks, in the parietal and temporal lobes respectively, should be more active during the CPT-IP relative to rest. I would expect that the effects of THC administration in the control group to be similar to those previously reported regarding acute THC administration. I would therefore expect to find a reduction in performance on the CPT-IP task relative to the placebo condition accompanied by decreased activation in the attentional networks. More specifically, since acute THC administration has been shown to affect the orienting and stimulus processing aspects of attention, I would expect the decrease in activation to be greatest in the ventral attentional network areas. In the nicotine-users placebo condition, I would expect to observe a mild impairment in attentional performance on the CPT-IP task, accompanied by reductions in the activation of the ventral attention network. Acute nicotine, in non-smokers, has been reported to have mild facilitative effects on attention, and withdrawal to have a detrimental effect in smokers. Given that during the CPT-IP task there would be no nicotine administration, this group would be seen as going through withdrawal from nicotine, causing the expected decrease in performance and activation of the ventral attention network. Finally, in nicotine-users under THC administration I would expect to find the greatest impairment in attentional performance. This would be due to the compounded effects of nicotine withdrawal and THC administration on attention described above. However, due to some overlap in the actions of nicotine and THC, it may be possible that the reduction in attentional performance and associated brain activation in this group under THC relative to placebo may not be as great as in the control group. That is to say that the effects of nicotine withdrawal and THC administration will not be completely additive, and there will be an interaction in the effects. These predictions are shown in the graph below, along an arbitrary scale of brain activation in the ventral attention network.



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