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Nicotinic–serotonergic interactions in brain and behaviour

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Abstract

This review focuses on nicotinic–serotonergic interactions in the central nervous system (CNS). Nicotine increases 5-hydroxytryptamine (5-HT) release in the cortex, striatum, hippocampus, dorsal raphé nucleus (DRN), hypothalamus, and spinal cord. As yet, there is little firm evidence for nicotinic receptors on serotonergic terminals and thus nicotine's effects on 5-HT may not necessarily be directly mediated, but there is strong evidence that the 5-HT tone plays a permissive role in nicotine's effects. The effects in the cortex, hippocampus, and DRN involve stimulation of 5-HT_{1A} receptors, and in the striatum, 5-HT_3 receptors. The 5-HT_{1A} receptors in the DRN play a role in mediating the anxiolytic effects of nicotine and the 5-HT_{1A} receptors in the dorsal hippocampus and lateral septum mediate its anxiogenic effects. The increased startle and anxiety during nicotine withdrawal is mediated by 5-HT_{1A} and 5-HT_3 receptors. The locomotor stimulant effect of acute nicotine is mediated by 5-HT_{1A} receptors and 5-HT_2 receptors may play a role in the expression of a sensitised response after chronic nicotine treatment. Unfortunately, the role of 5-HT_{1A} receptors in mediating nicotine seeking has not yet been investigated and would seem an important area for future research. There is also evidence for nicotinic–serotonergic interactions in the acquisition of the water maze, passive avoidance, and impulsivity in the five-choice serial reaction task. © 2002 Elsevier Science Inc. All rights reserved.

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1. Introduction

Most of the research on nicotine has focused on its effects on the dopaminergic system. However, because of the predominantly presynaptic localisation of the nicotinic receptors (nAChRs), nicotine induces the release of several other neurotransmitters, including acetylcholine (ACh), noradrenaline, serotonin [5-hydroxytryptamine (5-HT)], GABA, and glutamate (Wonnacott, 1997; Wonnacott et al., 1989; Role and Berg, 1996; Vizi and Lendvai, 1999). There is no direct evidence for presynaptic nicotinic receptors located on serotonergic nerve terminals, but as reviewed in this article, there is considerable evidence that nicotine does affect serotonergic neurotransmission. There are also several behavioural effects of nicotine that seem to be mediated by effects on the serotonergic system.

Although it is not the detailed subject of this review, it should be remembered that there is a complex bidirectional interaction between the cholinergic and serotonergic systems and that nicotine can influence the release of both ACh and serotonin. Thus, for example, in the dorsal hippocampus, stimulation of presynaptic nicotinic autoreceptors stimulates ACh release, through a nicotinic receptor that does not contain an α_7 subunit, whereas serotonergic stimulation of 5-HT_{1B} heteroreceptors decreases ACh release (Vizi and Kiss, 1998). Likewise, stimulation of the 5-HT_{1B} autoreceptors in the dorsal hippocampus decreases 5-HT release, whereas stimulation of nicotinic receptors increases 5-HT release (Lendvai et al., 1996; File et al., 2000b; Kenny et al., 2000b). Thus, as the serotonergic tone in this brain region is increased, the cholinergic tone is decreased, and vice versa. ACh release in the cortex is also decreased by 5-HT, acting through 5-HT_3 receptors in the cortex (Maura et al., 1992; Giovannini et al., 1998). Likewise, ACh release in the striatum is inhibited by serotonin acting at 5-HT_{1A} receptors (Rada et al., 1993). Thus, in several brain regions, there are likely to be mutually inhibitory effects between the cholinergic and serotonergic systems and any effects of nicotine will be the result of the balance of its effects on these two systems.

A number of different subtypes of nAChR exist, each with individual pharmacological and physiological profiles

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and distinct anatomical distribution in the brain. To date, nine individual subunits have been identified and cloned in the human brain. Studies have revealed that multiple subtypes of functional neuronal nAChRs can be formed from various combinations of nAChRs subunits, although evidence exists to suggest that nAChRs expressed in vivo may be functionally categorised into four groups (Zoli et al., 1998; Alkondon and Albuquerque, 1993) and the predominant forms in the central nervous system (CNS) are the $\alpha_4\beta_2$ and $\alpha_4\alpha_5\beta_2$ subtypes. Deficits in $\alpha_4\beta_2$ receptors have been associated with autism and schizophrenia and age-related neurodegenerative disorders have been predominantly associated with α_4-containing receptors (Court et al., 2000).

2. Nicotinic modulation of serotonergic transmission in the CNS

2.1. Cortex

Systematically administered nicotine (0.2 mg/kg sc) and the ($\alpha_4\beta_2$) nicotinic receptor agonist RJR-2403 significantly increased cortical 5-HT release in awake, behaving rats (Summers and Giacobini, 1995; Summers et al., 1996), whereas a higher dose (1.2 mg/kg sc) and other nonselective agonists like 5-fluoronicotine, noranhydroecgonine, and pyridyl-methylpyrrolidine were without any effect (Summers and Giacobini, 1995; Summers et al., 1995). Ribeiro et al. (1993) found that nicotine (1.6 mg/kg sc) significantly increased cortical 5-HT release, when the 5-HT uptake blocker, fluoxetine, was included in the perfusion medium, suggesting that the basal level of 5-HT might be important to nicotine's effects. Systematic nicotine (2–8 mg/kg sc) also increased extracellular 5-HT release in the frontal cortex of anaesthetised rats, but, in contrast to the long-lasting effect in awake rats, the effect was only transient (Ribeiro et al., 1993). Behavioural studies rarely use doses higher than 0.5 mg/kg and doses in excess of 1 mg/kg are likely to be having toxic effects. Because nicotine effects are dependent on the background tone of various neurotransmitters, it is also likely that different doses may be effective in vivo and in anaesthetised animals and in vitro.

Nicotinic binding sites have not been observed on serotonergic axons in the cortex (Schwartz et al., 1984). It has therefore been suggested that the increase in 5-HT release is likely to be due to stimulation of nicotinic receptors located on cortically projecting cell bodies in the dorsal raphé nucleus (DRN) (Summers and Giacobini, 1995; Summers et al., 1996). Furthermore, 5-HT levels were unaltered when nicotine (250 μM and 2.5 mM) was applied directly to the cortical tissue through the dialysis probe (Summers and Giacobini, 1995). However, administration of a high concentration (100 mM) of nicotine through dialysis probes in the cingulate and the frontal cortices did result in elevated levels of serotonin in these areas (Toth et al., 1992). This does not necessarily mean that nicotine was acting on a receptor located on the serotonergic terminal, as the effect could have been mediated indirectly via the release of another neurotransmitter.

The uptake of serotonin from the synaptic cleft by serotonin transporter proteins is the major mechanism for terminating the activity of the transmitter. Prenatal nicotine exposure (6 mg/kg/day; subcutaneous injection or infusion via osmotic minipump) has been shown to increase significantly the serotonin transporter density in the forebrain of juvenile rats (Muneoka et al., 2001). An earlier study had shown that prenatal nicotine exposure caused significant reductions of 5-HT turnover in the forebrain, cerebellum, and midbrain, although these effects appeared to be dependent upon the route of drug administration (Muneoka et al., 1997). Finally, nicotine has been found to modify 5-HT_{1A} receptor gene expression in the cortex. Nicotine (0.5 mg/kg ip) significantly increased the expression of 5-HT_{1A} receptor mRNA 2 and 24 h after acute administration, whereas receptor expression was decreased following 7 days of nicotine (0.5 mg/kg ip twice daily) treatment (Kenny et al., 2001).

2.2. Striatum

Recent immunocytochemical staining using confocal microscopy suggests that α_4 nicotinic receptor subunits and 5-HT_3 receptors are colocalised on nerve endings in the rat striatum (Nayak et al., 2000). This is the first direct evidence for colocalisation and this strengthens the possibility that nicotine might be having a direct effect on 5-HT release in this brain region. ACh, nicotine (0.3 μM and above), and the potent nicotinic receptor agonists epibatidine and cytisine, significantly increased [^{3}H]5-HT release from striatal synaptosomes, and this effect was blocked by the non-competitive nicotinic receptor antagonist, mecamylamine (Reuben and Clarke, 2000). The nicotine-stimulated increase in 5-HT release from striatal slices was significantly enhanced after 10 days of nicotine (1.76 mg/kg sc) treatment (Yu and Wecker, 1994) and the effects of chronic nicotine were enhanced by exposure to stress (Takahashi et al., 1998). Following 7 weeks of nicotine administered to mice in the drinking water, there were significant increases in concentrations of 5-HIAA, but not 5-HT, in the striatum (Gaddnas et al., 2000).

2.3. Hippocampus

Based largely on neuroanatomical evidence, the 5-HT innervation of the hippocampal formation comprises from serotonergic cell bodies located in the median raphé nucleus and the DRN. Whereas the median raphé projections innervate largely the dorsal hippocampal formation, the DRN projects heaviest to the ventral hippocampal formation (Mokler et al., 1998). The nicotinic receptor agonists, 1,1-dimethyl-4-phenylpiperazinium (DMPP) and lobeline, have been shown to increase [^{3}H]5-HT release

from rat hippocampal slices, although cytisine, epibatidine, and nicotine (10 and 100 μM) had no effect (Lendvai et al., 1996). Recently, Reuben and Clarke (2000) also found that nicotine (0.01–100 μM) had no effect on 5-HT release from hippocampal synaptosomes. However, Kenny et al. (2000b) found that exposure of rat dorsal hippocampal slices to nicotine (50–500 μM) increased the release of [^{3}H]5-HT in a concentration-dependent manner. The effect was antagonised by mecamylamine (0.5 μM), though higher concentrations of mecamylamine itself significantly increased 5-HT release, suggesting that mecamylamine blocks tonically active nAChRs located on cholinergic terminals and the resultant decreased release of ACh could unmask the M_1 muscarinic inhibitory mechanism on 5-HT release (File et al., 2000a,b; Kenny et al., 2000b). This can be further supported from the observation that the M_1 receptor antagonist, pirenzepine, increased hippocampal [^{3}H]5-HT release (Kenny et al., 2000b) (see Fig. 1 for diagrammatic representation). Finally, they suggested that the increase in 5-HT release will be seen only at high concentrations of nicotine (Kenny et al., 2000b). However, the effects may occur at lower concentrations in conditions, such as those of high anxiety, where glycine release is increased. Glycine (20 mM) significantly enhanced the effects of nicotine on potassium-evoked 5-HT release from dorsal hippocampal slices (File et al., 2000b). Once again there is no evidence that these effects of nicotine are the result of a direct action on presynaptic receptors located on serotonergic terminals.

Kenny et al. (2001) found that acute nicotine (0.5 mg/kg ip) significantly increased 5-HT_{1A} receptor mRNA in the CA3 and CA1 regions of the dorsal hippocampus 2 and 24 h after injection. The results suggest that regulation of 5-HT receptor expression may be one mechanism whereby nicotine acts to modulate 5-HT neurotransmission. There may be rapid tolerance to this effect of nicotine, since there was no longer any effect after 7 days of nicotine treatment (0.5 mg/kg ip twice daily). However, the increase in hippocampal 5-HT_{1A} receptor binding that was found in postmortem brains from smokers (Benwell et al., 1990) would suggest that, at least in some circumstances, these effects can persist after chronic nicotine exposure. Partial tolerance developed to the effects of nicotine on potassium-evoked release of 5-HT from hippocampal slices. After 6 days of nicotine (0.1 mg/kg/day sc) treatment, the effect of nicotine (50–200 μM) was significantly reduced, although a significant effect on 5-HT release still remained (Irvine et al., 2001b). In an in vivo microdialysis study, chronic treatment with nicotine (0.4 mg/kg sc for 21 days) decreased 5-HT concentrations in the dorsal hippocampus (Ridley and Balfour, 1997). This is in accord with the previous report of decreased hippocampal 5-HT concentration after chronic nicotine (0.4 mg/kg sc for more than 20 days) treatment (Benwell and Balfour, 1979). In contrast, Takada et al. (1995) reported increased 5-HT and 5-HIAA concentrations after chronic nicotine treatment (0.4 mg/kg/day sc for 14 days). They suggested that the effects of nicotine on the brain serotonergic system depended upon the duration of administration.

2.4. Dorsal raphé nucleus

Nicotine (10–300 μM) induced a concentration-dependent increase in serotonin release from rat midbrain slices which was accompanied by both increases and decreases of

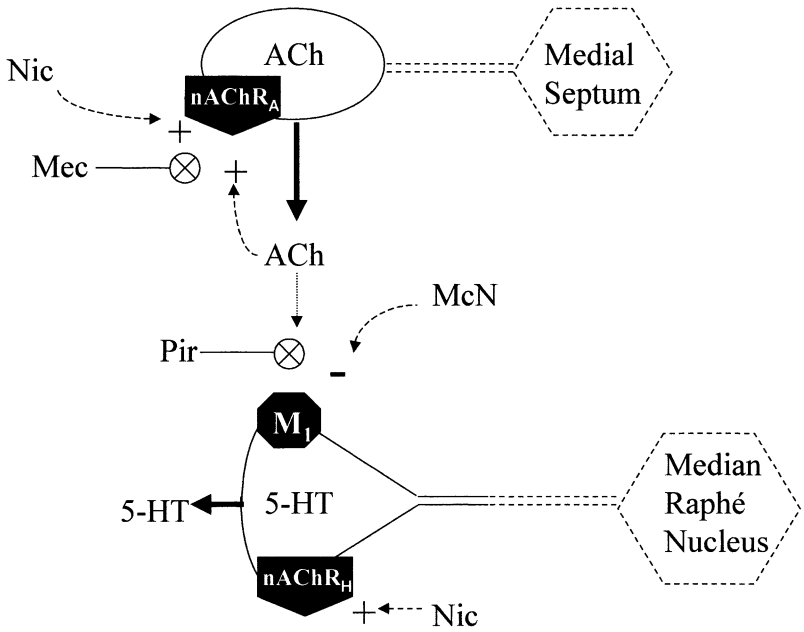

Fig. 1. Proposed model by which nicotinic receptor ligands might modulate 5-HT release in the dorsal hippocampus. $nAChR_A$, nicotinic autoreceptor; $nAChR_H$, nicotinic heteroceptor; M_1, muscarinic M_1 receptor; +, indicates stimulatory action; −, indicates inhibitory action; ⊗, indicates receptor antagonism; ACh, acetylcholine; 5-HT, 5-hydroxytryptamine; Nic, nicotine; Mec, mecamylamine; McN, McN-A-343; Pir, pirenzepine.

the firing rates of DRN neurones (Mihailescu et al., 1998). Serotonin release was much higher during the decrease in firing rates, which suggests an action of nicotine on presynaptic receptors of serotonergic neurones. When administered after nicotine, the nicotinic receptor antagonist, mecamylamine, initially reversed the stimulatory effects upon the firing rate and serotonin release, but later significantly increased both parameters. It is likely that direct excitatory and indirect inhibitory effects of nicotine both occur in the DRN and play opposite physiological roles (Mihailescu et al., 1998). Li et al. (1998) found that application of the nicotinic receptor agonist DMPP (15 μM) to DRN neurones in vitro induced both depolarising and hyperpolarising responses in the presence of atropine, which were blocked by mecamylamine. Furthermore, the DMPP-induced hyperpolarisation was blocked by the 5-HT_{1A} receptor antagonist pindobind, whereas the DMPP-induced depolarisation was mimicked by the α_1 receptor agonist phenylephrine, blocked by the α_1 receptor antagonist prazosin, and prolonged by the noradrenaline uptake inhibitor nisoxetine (Li et al., 1998). Thus, nicotinic receptor activation seemed to evoke the release of both noradrenaline and 5-HT and thereby activate both α_1 and 5-HT_{1A} receptors on DRN neurones. From these studies, Li et al. proposed that cholinergic fibres (from the cholinergic neurones of the laterodorsal and pedunculopontine nuclei) activated presynaptic nicotinic receptors located on both noradrenergic neurones from the locus coeruleus and serotonergic DRN neurones to facilitate release of noradrenaline and serotonin onto DRN neurones.

In anaesthetised rats, systemically administered nicotine (50–400 μg/kg iv) induced a transient inhibition of the majority of DRN 5-HT neurones (Engberg et al., 2000). The inhibition was also blocked with a selective 5-HT_{1A} receptor antagonist, WAY 100635 (0.1 mg/kg iv), indicating that nicotine increases 5-HT release and that a possible somatodendritic 5-HT_{1A} autoreceptor is involved in the effect of nicotine. Interestingly, microiontophoretic application of nicotine (2.5–20 nA) into the DRN failed to inhibit 5-HT neurones, suggesting an indirect effect of nicotine on 5-HT neurones, possibly by involving afferent pathways (Engberg et al., 2000). When rats were withdrawn after 12 days of nicotine treatment (6 mg/kg/day via osmotic minipumps), an increased sensitivity to 8-OH-DPAT was observed in serotonergic neurones in the DRN in anaesthetised rats (Rasmussen and Czachura, 1997).

Guzman-Marin et al. (2001) found that nicotine (0.1 mg/kg sc) increased the discharge rate of DRN serotonergic neurones during REM sleep, without any significant change during non-REM sleep or waking. Since 5-HT-containing neurones in the DRN virtually cease firing when an animal starts REM, consequently decreasing the release of 5-HT during this state (Monti and Monti, 2000), the above findings again provide evidence that the basal 5-HT tone may be important to the effects of nicotine.

2.5. Hypothalamus

Both acute and chronic systemic administration of nicotine in rats increase 5-HT levels in the hypothalamus (Dominiak et al., 1984; Kirch et al., 1987; Takada et al., 1995), although the rates of 5-HT synthesis were unaffected (Mitchell et al., 1989). In mice exposed to 7 weeks of increasing doses of nicotine in the drinking water, there was no change in 5-HT concentrations, but there was a significant increase in 5-HIAA concentrations that lasted for 24 h after nicotine was withdrawn (Gaddnas et al., 2000). Miyata et al. (1999) found that systemic nicotine infusion in rats for 7 days caused an increase of 5-HT (and dopamine) in the lateral hypothalamus measured by in vivo microdialysis, and an accompanying hypophagia. In subsequent studies, they observed that lateral hypothalamic nicotine (4 mM) infusion via reverse microdialysis technique suppressed food intake and considerably increased hypothalamic 5-HT levels during the entire nicotine administration period (Yang et al., 1999). In their recent studies, they demonstrated that chronic nicotine administration decreased food intake and this could be related to an increase in both dopamine and serotonin activity in the lateral hypothalamus and the ventromedial nucleus (Meguid et al., 2000).

2.6. Spinal cord

The interactions between cholinergic and serotonergic systems have been examined using mouse spinal slices. Application of nicotine and cytisine (30–300 μM) increased the basal release of [^{3}H]5-HT in a dose-dependent manner. The nicotine-elicited increase in 5-HT release was significantly attenuated after preincubation with the nicotinic receptor antagonists mecamylamine (30 μM), dihydro-β-erythroidine (DHβE, 50 μM), or hexamethonium (200 μM), although, when applied alone, all of these antagonists enhanced the release of [^{3}H]5-HT (Cordero-Erausquin and Changeux, 2001). This is similar to the pattern found in the dorsal hippocampus (Kenny et al., 2000b). In contrast, methyllycaconitine (MLA, 40 nM), at a concentration considered to block α_7 subunit containing nAChRs, potentiated the response to nicotine and was also ineffective per se (Cordero-Erausquin and Changeux, 2001).

Overall, these experiments suggest the existence of multiple populations of functional nAChRs controlling, directly or indirectly, serotonin release in the spinal cord. The first, activated by agonist application, has an excitatory outcome and could be directly located in serotonergic terminals; the second, tonically activated by endogenous ACh and inhibited by nicotinic receptor antagonists, has an inhibitory outcome and is present in inhibitory neurones. Finally, the data on MLA suggest that there is a third nAChRs population which is not tonically activated, but is also present in inhibitory neurones and has an inhibitory effect on 5-HT release (Cordero-Erausquin and Changeux, 2001). Nicotine was able to enhance 5-HT release in α_4 and β_2 knock-out

mice (Cordero-Erausquin and Changeux, 2001), suggesting that the nAChRs, which increase 5-HT release, do not contain either α_4, β_2, or α_7 subunits. This result is consistent with previous electrophysiological data obtained in α_4 and β_2 knock-out mice (Marubio et al., 1999), which revealed the presence of presynaptic (non-α_4 and -β_2) nAChRs in the dorsal horn of the spinal cord. Thus, it appears that nAChRs involved in the positive control of 5-HT release in the spinal cord have a unique composition and may be different form those expressed in the brain and ganglia.

3. Nicotinic–serotonergic interactions in the modulation of anxiety

3.1. Dorsal raphé nucleus

The DRN has been identified as an important neuroanatomical substrate mediating nicotine's anxiolytic effect. Low doses of nicotine (2.5–10 ng) administered directly into the DRN induced an anxiolytic effect in the social interaction test of anxiety (Cheeta et al., 2001a). This is similar to the pattern previously observed when the specific 5-HT_{1A} receptor agonist 8-OH-DPAT was administered to this region (Higgins et al., 1988; Hogg et al., 1994; Picazo et al., 1995). The anxiolytic effects of nicotine was completely antagonised by coadministration into the DRN of behaviourally inactive dose of the 5-HT_{1A} receptor antagonist, WAY 100635 (Cheeta et al., 2001a). This suggests that the anxiolytic effect of nicotine is mediated by increasing 5-HT release in the DRN, which stimulates the 5-HT autoreceptors, leading to a reduction in 5-HT neuronal firing and a subsequent decrease in 5-HT release in terminal regions of the limbic system (Sprouse and Aghajanian, 1987).

The anxiolytic effect of intra-DRN nicotine is completely reversed by a silent dose of the $\alpha_4\beta_2$ nicotine receptor antagonist, DHβE (Cheeta et al., 2001b). This suggests that the nicotine-induced 5-HT release is mediated by presynaptic high-affinity nicotinic receptors, probably of the $\alpha_4\beta_2$ subtype. An involvement of this receptor subtype in 5-HT release in the DRN would be consistent with the finding that nicotine-elicited currents could not be evoked from 5-HT neurones in the DRN in mice lacking both or either of the α_4 and β_2 subunits. (Cordero-Erausquin et al., 2000).

3.2. Lateral septum

In contrast to the pattern observed in the DRN, when injected into the lateral septum, nicotine (1 and 4 μg) had anxiogenic effects in both the social interaction and the elevated plus-maze tests (Ouagazzal et al., 1999). Similar anxiogenic effects were observed after bilateral injection of 8-OH-DPAT into the lateral septum and the effects of both nicotine and 8-OH-DPAT were antagonised by concomitant administration of WAY 100635 into the lateral septum (Cheeta et al., 2000a). This suggests that the effects of nicotine were indirectly mediated by stimulating postsynaptic 5-HT_{1A} receptors. However, the effects of the highest dose of nicotine (8 μg) were only partially antagonised by WAY 100635, which raises the possibility that nicotine might also have anxiogenic effects through the release of another neurotransmitter in this region, such as noradrenaline.

The effects of mecamylamine when administered into the lateral septum revealed the presence of an endogenous cholinergic tone acting to increase anxiety. Thus, a low dose of mecamylamine (15 ng) had a significant anxiolytic effect. This cholinergic tone was not maximal since it could be further enhanced by the administration of nicotine, resulting in an anxiogenic effect. This could explain why the anxiogenic effect of nicotine could not be reversed by 30 ng of mecamylamine (which had no effects when given alone), but could be reversed by a higher (50 ng) dose (Ouagazzal et al., 1999). At an even higher dose (100 ng), mecamylamine had a significant anxiogenic effect (File et al., 2000a). This might indicate the presence of a second population of nAChRs in this brain region at which endogenous cholinergic tone serves an anxiolytic function. Alternatively, the effects of this high dose of mecamylamine might be due to its antagonist action on the NMDA receptors. The cholinergic system interacts with many other neurotransmitter pathways and while there is evidence that nicotine's anxiogenic effects in the lateral septum are mediated via the 5-HT system, this has not been tested for mecamylamine in this brain region. It is possible that the anxiogenic effect of mecamylamine is mediated by indirectly increasing 5-HT release and the anxiolytic effect is mediated by antagonising endogenous cholinergic tone on nicotinic heteroreceptors. However, these heteroreceptors may not be on 5-HT terminals and interaction with other transmitters such as noradrenaline cannot be ruled out.

3.3. Dorsal hippocampus

In the social interaction test of anxiety, low doses of nicotine (0.5–5 ng) were ineffective when administered directly to the dorsal hippocampus (Cheeta et al., 2000b), whereas higher doses (0.1–8 μg) were anxiogenic (File et al., 1998b). However, the anxiogenic effect of nicotine was dependent on the test condition. In conditions of low and high anxiety, nicotine was without effect, whereas in the two conditions of moderate anxiety it had anxiogenic effects. The nicotinic receptor antagonist mecamylamine (30 and 100 ng administered directly into the dorsal hippocampus) had anxiogenic effects in the test condition generating low anxiety, but was silent in the conditions of moderate and high anxiety (File et al., 1998a, 2000a). In the conditions of low anxiety, the M_1 muscarinic receptor antagonist, pirenzepine, also had an anxiogenic effect (File et al., 1998a). This suggests that in conditions of low anxiety, there is endogenous cholinergic tone acting to reduce anxiety, but that this tone is reduced in conditions of higher anxiety. The anxiogenic effects of both nicotine and mecamylamine were

reversed by WAY 100635, implicating a role for the postsynaptic 5-HT_{1A} receptors (File et al., 2000b; Kenny et al., 2000a). This would be in accord with the findings that both nicotine and mecamylamine can increase 5-HT release from dorsal hippocampal slices (Kenny et al., 2000b). These two effects are likely to be mediated at two distinct nAChRs in the dorsal hippocampus, with mecamylamine acting at nicotinic autoreceptors on cholinergic terminals and nicotine acting at a heteroreceptor on the serotonergic terminal (if these exist) or indirectly via release of another neurotransmitter. Further evidence that nicotine and mecamylamine are acting at different receptor populations comes from the effects of glycine, which enhances the nicotine-stimulated 5-HT release, by a strychnine-sensitive mechanism, but blocks the mecamylamine-induced 5-HT release by a strychnine-insensitive mechanism. The effects of mecamylamine are most readily seen in conditions of low anxiety, where there is high endogenous cholinergic tone and those of nicotine are expressed in conditions of increased serotonergic and glycinergic tone (see File et al., 2000b).

3.4. Nicotine withdrawal

Rats withdrawn from chronic treatment with nicotine show anxiogenic responses in the social interaction and elevated plus-maze tests (Irvine et al., 1999, 2001a; Cheeta et al., 2001), and an enhanced auditory startle response (Rasmussen et al., 1997). Mice withdrawn from chronic treatment with nicotine show an anxiogenic response in the light–dark crossing test (Barnes et al., 1990; Costall et al., 1990). The anxiogenic withdrawal response in the mouse was reversed by systemic administration of 5-HT_3 receptor antagonists (Barnes et al., 1990) and the enhanced auditory startle was reversed by systemic administration of 5-HT_{1A} receptor antagonists and was exacerbated by the 5-HT_{1A} receptor agonist, 8-OH-DPAT (Rasmussen et al., 1997). The 5-HT_{1A} receptor partial agonist, buspirone, alleviated the enhanced anxiety experienced by smokers during withdrawal (West et al., 1991).

So far, two brain regions have been identified as mediating nicotine withdrawal effects on anxiety. Nicotine (5 ng) administered into the DRN reversed the anxiogenic withdrawal response detected in the social interaction test (Cheeta et al., 2001a) and the 5-HT_3 receptor antagonist, ondansetron, administered into the DRN reversed the anxiogenic withdrawal response in the light–dark crossing test (Costall et al., 1990). This makes it likely that the DRN is a primary site of action of the systematically administered 5-HT_3 receptor antagonists. However, it would seem unlikely that the DRN was the site of action of the 5-HT_{1A} receptor ligands, given the pattern of their effects. It would seem more likely that they were acting at one or more of the raphé terminal regions, where stimulation of postsynaptic 5-HT_{1A} receptors has anxiogenic effects. The dorsal hippocampus would be one possibility, since a low dose of nicotine (5 ng), ineffective in control rats, administered to this region reversed the anxiogenic withdrawal response detected in the elevated plus-maze (Irvine et al., 2001a).

4. Nicotinic–serotonergic interactions in stimulant and rewarding effects

4.1. Locomotor stimulation

Acute doses of nicotine can cause small increases in locomotor activity, but the stimulant effects are much greater after a period of chronic administration when there is sensitisation to this response (e.g., Benwell and Balfour, 1992; Clarke et al., 1988). The stimulant effects are probably mediated by activation of postsynaptic dopamine receptors in the nucleus accumbens (Benwell and Balfour, 1992; Clarke et al., 1988). Systemic administration of 8-OH-DPAT (0.5 mg/kg sc) potentiated the stimulant effect of acute nicotine (1 mg/kg sc). Changing 5-HT tone by depleting the levels with 5,7-DHT, or augmenting it with administration of the selective serotonin uptake inhibitor citalopram, did not change the locomotor stimulation caused by an acute dose of nicotine (Olausson et al., 1999). However, modifications of 5-HT tone did modify the sensitisation of locomotor stimulation. The locomotor stimulant effect of chronic nicotine was decreased by treatment with *para*-chlorophenylalanine (pCPA), which depletes 5-HT (Fitzgerald et al., 1985; Olausson et al., 1999) and by increased 5-HT tone caused by chronic treatments with the selective serotonin uptake inhibitor, citalopram or the 5-HT_2 receptor agonist, DOI (Olausson et al., 1999). Thus, both increases and decreases in 5-HT tone prevented the expression of locomotor stimulation, suggesting that this effect of nicotine was only manifested in conditions of moderate tone. This is similar to the effects of nicotine on anxiety, which were expressed in conditions generating moderate anxiety and not in conditions of very high or very low tone (File et al., 2000b).

There is some evidence that 5-HT_3 receptors might be involved in the stimulant effects of chronic nicotine, as pretreatment with high doses of MDL 72222 and tropisetron (1 mg/kg sc) significantly reduced this effect (Arnold et al., 1995; Corrigall and Coen, 1994). However, lower doses of a wide range of 5-HT_3 receptor antagonists failed to antagonise nicotine's locomotor stimulant effects, suggesting that 5-HT_3 receptors are unlikely to be the main target for modulating these effects. A role for 5-HT_4 receptors can also be excluded. Reavill et al. (1998) pretreated animals with nicotine (0.4 mg/kg sc for 8 days), but the 5-HT_4 receptor antagonist SB-2040707-A (0.1–3 mg/kg ip) failed to antagonise the resulting hyperactivity. A recent experiment provided evidence that 5-HT_{2C} receptors might be involved in the increased locomotor activity following nicotine sensitisation. Ro 60-0175, a 5-HT_{2C} receptor agonist, dose-dependently blocked the increased activity (Grottick et al., 2001).

4.2. Place preference, self-administration, and self-stimulation

Although place preference conditioning to nicotine has been observed, studies have suggested that this paradigm may not be a robust test for measuring the reinforcing effects of nicotine compared with other drugs such as amphetamine, cocaine, or morphine (Jorenby et al., 1990; Parker, 1992; Shippenberg et al., 1996). However, recent studies suggest that strain and nicotine dose are important factors in establishing nicotine-induced place preference conditioning (Risinger and Oakes, 1995; Horan et al., 1997). A clearer role for 5-HT_3 receptors can be found in mediating nicotine's effects in tests of place preference. Place preference conditioning was established using a training dose of 0.6 mg/kg nicotine and the preference for the nicotine-associated side was dose-dependently antagonised by the 5-HT_3 receptor antagonists ICS 205-930 and MDL 72222 (Carboni et al., 1988). This antagonism was most likely to be due to an action on 5-HT_3 receptors to modify dopamine release, since ICS 205-930 antagonised the nicotine-induced stimulation of dopamine release in the nucleus accumbens in freely moving rats (Carboni et al., 1989), and 5-HT_3 receptor agonists caused dopamine release in the nucleus accumbens (Chen et al., 1991; Jiang et al., 1990). These results again suggest that 5-HT tone might play a permissive role in the expression of nicotine's effects.

When withdrawal from nicotine was precipitated with mecamylamine, this induced a place aversion, which was dose-dependently attenuated by pretreatment with the 5-HT_3 receptor antagonist ondansetron (Suzuki et al., 1997). This result suggests that antagonism of the 5-HT_3 receptors may alleviate the aversive state induced by nicotine withdrawal, and these findings are consistent with the observations by Costall et al. (1990) that ondansetron attenuated the anxiogenic effect of nicotine withdrawal in mice. These results from place preference suggest that increased dopamine release is equally important in signalling an aversive state as it is in signalling reward. There is some evidence for an involvement of 5-HT_{2C} receptors in nicotine self-administration, since a relatively high dose of Ro 60-175 (1 mg/kg), a 5-HT agonist, reduced self-administration (Grottick et al., 2001).

In contrast to the effects on place preference, Corrigall and Coen (1994) found that the 5-HT_3 receptor antagonists ICS 205-930 and MDL 72222 did not affect nicotine self-administration. These findings are in agreement with clinical findings that smoking is unaffected by treatment with 5-HT_3 receptor antagonists (Park et al., 1993; Zacny et al., 1993). Furthermore, the findings suggest that there may be important differences among the various tests purporting to measure the rewarding aspects of drugs, and that each test may reflect different aspects of reward.

Montgomery et al. (1993) found that acute administration of nicotine (0.4 mg/kg ip) initially depressed self-stimulation in the lateral hypothalamus, but that this was followed by a period of facilitated responding. Following chronic nicotine treatment, there was sensitisation to this effect of facilitated responding. Ondansetron (100 μg/kg sc) reduced the initial depression of self-stimulation by an acute dose of nicotine, but not the ensuing facilitation or the sensitised facilitation. Ivanova and Greenshaw (1997) found chronic nicotine (0.6 mg/kg) reduced the threshold for ventral tegmental area self-stimulation and this effect was antagonised by mecamylamine (1.0 mg/kg sc), but not by the muscarinic receptor antagonist scopolamine (3 mg/kg sc) or the 5-HT_3 receptor antagonist ondansetron (0.01 and 0.1 mg/kg sc).

4.3. Nicotinic–serotonergic interaction in cognition

While there is evidence that an intact cholinergic system is essential for cognitive processes such as learning and memory (Hagan and Morris, 1988; Steckler and Sahgal, 1995), it is unlikely that ACh is the only neurotransmitter important for cognition and several studies have addressed possible serotonergic–cholinergic interactions. The ascending cholinergic and serotonergic systems project partially to the same regions of the forebrain, and serotonergic axons innervate the cholinergic nuclei in basal forebrain and brainstem; conversely, cholinergic axons from the brainstem nuclei innervate the raphé nuclei (Decker and McGaugh, 1991; Cassel and Jeltsch, 1995; Steckler and Sahgal, 1995). Interactions have been reported between muscarinic receptors and the serotonergic system (Sakurai and Wenk, 1990; Riekkinen and Riekkinen, 1995; Riekkinen et al., 1991; Santucci et al., 1995), but this review has focused on the interactions between nicotinic receptors and serotonin in mediating cognition.

In humans, the most robust demonstrations of nicotine-related improvements in cognition are seen in tasks that measure attention (Wesnes and Warburton, 1978; Foulds et al., 1992; Heishman, 1998). In a test of working memory in animals, the delayed-nonmatching-to-position task (DNMTP task), a specific impairment in working memory, is revealed by the absence of deficits at short delays and greater deficits as the interval between the stimulus and response is increased. Delay-independent effects indicate some non-mnemonic change, for example, in attention. Combined 5,7-DHT lesions of the median raphé nucleus and DRN (Sahgal and Keith, 1993), or depletions of the serotonergic system using pCPA (Jakala et al., 1993), intracerebroventricular 5,7-DHT (Ruotsalainen et al., 1997), or pCA (Ruotsalainen et al., 1998) did not result in significant impairments in this task. However, a high dose of mecamylamine (3 mg/kg) significantly impaired performance in a delay-independent manner, suggesting a non-mnemonic effect, but this did not interact with the serotonergic lesions (Ruotsalainen et al., 1997, 1998).

Mecamylamine (10 mg/kg ip) significantly impaired the acquisition of a water maze and this impairment was more marked in animals depleted of serotonin by pCPA injections

(Riekkinen et al., 1992). The combination of subeffective doses of 8-OH-DPAT and mecamylamine (2.5 mg/kg ip) impaired acquisition, but not consolidation or retrieval of a water maze, suggesting that the impairment was not of memory, but perhaps of attention (Riekkinen et al., 1994a). The impairment was exacerbated in pCPA-treated rats, but it is not possible to be sure whether the effects of 8-OH-DPAT in these rats were mediated by pre- or postsynaptic 5-HT_{1A} receptors. However, combined cholinergic and serotonergic denervation of the forebrain, produced by a radiofrequency lesion of the septum and intracerebroventricular 5,7-DHT produced extremely severe deficits in acquisition of the water maze (Nilsson et al., 1988). Electrolytic lesions of the medial septal nucleus impaired acquisition of the water maze, but the deficit was greatly reduced by nicotine (0.3 mg/kg ip). However, this beneficial effect of nicotine was not seen in animals with combined medial septal lesions and serotonin depletion following pCPA injection (Riekkinen et al., 1994b). Thus, the beneficial effects of nicotine on attentional processes may crucially involve an action on 5-HT neurones. In contrast to the pattern seen with septal lesions, lesions of the nucleus basalis did not significantly impair acquisition of the water maze, either alone or in combination with pCPA treatment (Riekkinen and Riekkinen, 1995). However, combined lesions of the medial septum and the nucleus basalis did produce transient impairments in water maze acquisition and retention. These effects were reversed by nicotine and arecoline, at doses that also improved performance in unlesioned rats and by WAY 100289, a 5-HT_3 receptor antagonist, that was ineffective when given to control rats (Hodges et al., 1995).

Riekkinen et al. (1992) investigated the effects of mecamylamine and serotonin depletion with pCPA in the passive avoidance test. Mecamylamine had no effect when administered alone, but combined treatment with mecamylamine and pCPA impaired acquisition. Medial septal lesions impaired behaviour in passive avoidance and the effect of the lesion was aggravated with treatment with pCPA (Riekkinen et al., 1994b). As was found in the water maze, although nicotine treatment alleviated the impairment in the rats with the medial septal lesions alone, the therapeutic effects of nicotine were no longer seen in animals with combined medial septal lesions and pCPA treatment. However, in contrast to the lack of effects in the water maze, rats with lesions of the nucleus basalis showed impaired passive avoidance memory and this was improved by treatment with nicotine (0.1 and 0.3 mg/kg). The impairment in passive avoidance in nucleus basalis-lesioned rats was further aggravated by treatment with pCPA, but nicotine was no longer effective in the combined lesion animals. The finding that the combined lesion affected passive avoidance more than the nucleus basalis lesion alone supports the notion that basal forebrain cholinergic and brainstem serotonergic systems interact to regulate behavioural functioning.

The five-choice serial reaction time task is a task designed to measure attentional processing and it thus provides a more direct approach to whether nicotine is acting to improve attention. Grottick and Higgins (2000) showed that subchronic treatment with nicotine (0.2 mg/kg sc) significantly improved performance on this task (shown by an increased percentage of correct choices and by a reduced latency to make the correct choice), as did the $\alpha_4\beta_2$ agonist, SIB 1765F, but not the α_7 agonist AR-R 17779. Nicotine and SIB 1765F also increased the incidence of premature responding. The noncompetitive nicotinic receptor antagonist, mecamylamine (0.3–3 mg/kg sc), impaired performance in this test by decreasing the percentage of correct choices and increasing the latency to make a correct choice; mecamylamine also decreased the incidence of premature responding. The last two effects were also found by Ruotsalainen et al. (2000), who also found that the effect of mecamylamine on premature responding was less marked in 5,7-DHT-lesioned rats, although mecamylamine's effects on choice accuracy were not affected by the lesion. This suggests that nicotinic modulation of impulsivity was also modulated by 5-HT tone, but that its effects on choice accuracy were not. It is also possible that mecamylamine's effect to impair accuracy in this task was not mediated by an action on nicotinic receptors, since the high-affinity competitive receptor antagonist DHβE (1–10 mg/kg sc) was without effect (Grottick and Higgins, 2000). This effect of mecamylamine could have been mediated by its action on NMDA receptors (O'Dell and Christensen, 1988).

5. Conclusions

There is good evidence that nicotine increases 5-HT release in several brain regions, although there is as yet little evidence that this is the result of a direct effect of nicotine on presynaptic heteroreceptors on 5-HT terminals. However, it is clear that the 5-HT tone plays a crucial permissive role in the expression of nicotine's effects and this can be seen at the level of 5-HT release and on nicotine's effects on cognition. This is important because it means that results from in vitro preparations or electrophysiological recordings from anaesthetised animals may not provide results that are pertinent to the in vivo conditions pertaining in animal tests.

In several behaviours, including tail tremor (Suemaru et al., 2000), anxiety (File et al., 2000a,b; Cheeta et al., 2001a), and startle (Rasmussen et al., 1997), there is good evidence that the effects of nicotine are mediated by 5-HT_{1A} receptors. Although 5-HT_3 receptors are involved in mediating nicotine-induced place preference (Carboni et al., 1989), they do not seem to be involved in other measures of nicotine's rewarding effects. The possible role of 5-HT_{1A} receptors in mediating nicotine-seeking behaviour has not been investigated. This is a great pity since the 5-HT_{1A} receptor antagonist, WAY 100635 (but not the 5-HT_2 receptor antagonist, ritanserin), has been shown to reduce

cocaine seeking (Schenk, 2000). Bupropion has been shown to reduce nicotine craving during smoking cessation (Hurt et al., 1997; Jorenby et al., 1999), but although it had been assumed that its mode of action was by blocking dopamine reuptake, this does not seem to be the case, because bupropion's affinity for dopaminergic and noradrenergic reuptake blockade is in the high micromolar range (Ferris et al., 1981) and such concentrations are unlikely to be achieved with the doses in clinical use. Since bupropion is a noncompetitive nicotinic receptor antagonist (Fryer and Lukas, 1999; Slemmer et al., 2000), acting preferentially at $\alpha_3\beta_2$ subtypes, this could be its primary site of action.

The strongest evidence is for nicotinic effects mediated by 5-HT_{1A} receptors and it is interesting that both nicotine and 5-HT_{1A} receptor agonists can have anxiolytic and antidepressant actions. However, the antidepressant actions of both compounds may be importantly linked to their anxiogenic effects that are evident at higher doses, rather than to their low-dose anxiolytic actions.

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