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The influence of lobeline on nucleus accumbens dopamine and locomotor responses to nicotine in nicotine-pretreated rats

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1 *In vivo* brain microdialysis was used to investigate the influence of lobeline on dopamine (DA) and dihydroxyphenylacetic acid (DOPAC) overflow in the core of the nucleus accumbens of freely-moving rats pretreated with nicotine (0.4 mg kg^{-1}, s.c., once per day for 5 days). Locomotion was also recorded.

2 Lobeline, at doses of 0.7, 4.0 and 10.0 mg kg^{-1}, i.p., failed to elicit any significant changes in extracellular dopamine or dihydroxyphenylacetic acid levels during the 60 min following its administration and did not stimulate locomotor.

3 The dopamine responses to nicotine (0.4 mg kg^{-1}, s.c.), were abolished ($P<0.01$) if the nicotine challenge was administered 10 min but not 60 min, after lobeline doses of 4.0 and 10.0 mg kg^{-1}, i.p., but were unaffected following lobeline at the lowest dose tested (0.7 mg kg^{-1}, i.p.) at either time. The increase in locomotor activity was significantly attenuated ($P<0.01$), to a similar extent, when the nicotine was injected 10 min, but not 60 min, after all three doses of lobeline (0.7, 4.0 and 10.0 mg kg^{-1}, i.p.) when compared with the saline-treated rats.

4 The results suggest that lobeline is a short-acting antagonist of the nicotinic AChRs which mediate the effects of nicotine on mesolimbic dopamine activity and locomotor stimulation.

Keywords: Lobeline; nicotine; nucleus accumbens; locomotion; microdialysis

Introduction

Lobeline is a naturally occurring alkaloid obtained from the Asian plant, *Lobelia inflata*. It is generally considered to be an agonist at the neuronal nicotinic cholinoceptors (AChRs) present on both peripheral autonomic ganglia (Jaramilo & Volle, 1968; Nooney *et al*., 1992) and in the central nervous system and has been used as substitution therapy to aid in the cessation of tobacco smoking (Nunn-Thompson & Simon, 1989; Olin *et al*., 1995). Lobeline binds with relatively high affinity to nicotinic binding sites in brain tissue (Reavill *et al*., 1988; Anderson & Arneric, 1994; Damaj *et al*., 1997) and it has been reported to have many nicotine-like qualities. For example, lobeline has been shown to have anxiolytic activity (Brioni *et al*., 1993), enhance cognition (Decker *et al*., 1993), produce hyperalgesia (Harmann & Martin, 1994), enhance latent inhibition under some conditions (Rochford *et al*., 1996), and stimulate neurotransmitter release in the brain (Clarke & Reuben, 1996; Lendvai *et al*., 1996; Sershen *et al*., 1997; Teng *et al*., 1997). However, in contrast to nicotine, lobeline does not increase locomotion (Stolerman *et al*., 1995), generalize to a nicotine discriminative stimulus (Reavill *et al*., 1990; Brioni *et al*., 1993) or produce conditioned place preference (Fudala & Iwamoto, 1986). Lobeline, therefore, does not share all the pharmacological properties of nicotine.

The positive reinforcing effects of nicotine, as demonstrated by self-administration studies (Singer *et al*., 1982; Corrigall *et al*., 1992, 1994; Donny *et al*., 1995), are believed to be mediated by increased dopamine (DA) overflow in the mesolimbic system of the brain (Corrigall *et al*., 1992, 1994). It has also been suggested that this same neural pathway plays a role in mediating the effects of nicotine as a discriminative stimulus (Stolerman & Reavill, 1989) and the locomotor stimulant properties of the drug (Clarke *et al*., 1988) although the latter is somewhat controversial (Vezina *et al*., 1994). Nicotine produces these effects by activating centrally-located nicotinic AChRs (Imperato *et al*., 1986; Benwell *et al*., 1995). Nicotinic receptors are present at both the somatodendritic and terminal regions of the mesolimbic DA neurones (Clarke & Pert, 1985). However, there is convincing evidence that the receptors located on the cell bodies of these neurones, in the ventral tegmental area of the midbrain, mediate the stimulant effects of nicotine on this system (Benwell *et al*., 1993; Nisell *et al*., 1994). To our knowledge, the effects of lobeline on nucleus accumbens DA secretion, *in vivo*, have not been investigated. Therefore, the present study used the technique of *in vivo* brain microdialysis, in conscious freely moving rats, to address the question of the influence of lobeline on mesolimbic DA secretion and locomotor activity. These studies were carried out in nicotine-pretreated rats since the intention was also to investigate the influence of lobeline upon nicotine-induced responses which have previously been demonstrated to be enhanced following repeated intermittent pretreatment with nicotine (Benwell & Balfour, 1992; Balfour *et al*., 1998).

Methods

Male Sprague-Dawley rats, bred by the Biomedical Services Unit, University of Dundee, from stock obtained commercially from Interfauna and weighing 200–250 g at the start of the experiment, were used throughout. The rats were housed in pairs prior to and singly after surgery.

All animals in this study were pretreated with nicotine (0.4 mg kg^{-1}, s.c.) once per day for 5 days to sensitize them to nicotine (Benwell & Balfour, 1992). Full details of the dialysis probe and its implantation have been described previously (Benwell & Balfour, 1992). In brief, at least 3 h after their injection on day 5, dialysis probes were implanted, under

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halothane anaesthesia, using the co-ordinates of 1.7 mm anterior, 1.5 mm lateral to Bregma and 7.5 mm vertically from the surface of the brain according to Paxinos and Watson (1986), co-ordinates which place the dialysis tip in the core of the NAc. The core was specifically chosen for this study because our previous studies on sensitization to nicotine have focused on the DA secretion in this subdivision of the NAc which sends major projections to areas of the brain implicated in the regulation of motor behaviour (Heimer *et al*., 1991). Eighteen hours following implantation of the dialysis probe. The animals were placed individually in activity boxes (40 cm × 40 cm × 25 cm high) in which the locomotor response was assessed by photocells located on adjacent sides of the box as described by Vale and Balfour (1989). At this time, the dialysis probes were connected to a syringe pump containing a Ringer solution (147 mM NaCl; 1.25 mM $CaCl_2$ and 4.0 mM KCl) and perfused at a rate of 1.7 μl min^{-1}. The rats were allowed to equilibrate for at least 1 h. Following this interval, three 20-min samples were collected to establish the baseline extracellular levels of DA and dihydroxyphenylacetic acid (DOPAC) release. At this time, different groups of rats received intraperitoneal injections of either saline (1 ml kg^{-1}) or lobeline (0.7, 4.0 or 10.0 mg kg^{-1}) followed by a subcutaneous challenge injection of nicotine (0.4 mg kg^{-1}) 10 min later. The dialysate was not collected during the 10 min interval between the two injections. A further six 20 min samples were collected after the nicotine injection.

In a separate experiment and using different groups of nicotine-pretreated rats, the rats were given the nicotine challenge 60 rather than 10 min after receiving intraperitoneal injections of either saline (1 ml kg^{-1}) or lobeline (0.7, 4.0 or 10.0 mg kg^{-1}). Dialysate samples were collected at 20-min intervals throughout and a further six samples collected after the nicotine injection. The levels of DA and DOPAC in the dialysates was measured by HPLC in combination with a Coulochem electrochemical detector. The position of the probes was routinely determined histologically from sections prepared at post-mortem and any animals with probes located outside the core of the NAc were excluded.

Drugs

(−) Nicotine hydrogen tartrate (dissolved in isotonic saline and adjusted to pH 7.0 by the addition of a small quantity of NaOH for injection) and (L)-lobeline hemisulphate (dissolved in isotonic saline) were obtained commercially from the Sigma Chemical Company. All doses quoted are of the free base concentration. EDTA was purchased from Fisons PLC; h.p.l.c. grade methanol and water from Rathburn Chemical Ltd. All other h.p.l.c. grade reagents were purchased from British Drug Houses.

Statistical analysis

The data were analysed by analysis of variance (ANOVA) for repeated measures using the Statistical Package for Social Scientists (SPSS). In the experiment in which the rats were challenged with nicotine 10 min after saline or lobeline, the data were initially analysed by a global four level analysis with the responses to saline and the three doses of lobeline as one of the independent factors analysed with samples taken from 20–190 min as the repeated measures. In the experiment in which the rats were challenged with nicotine 60 min after saline or lobeline, samples collected from 20–120 min were initially analysed by a global four level analysis with the responses to saline and the three doses of lobeline as one of the independent factors analysed to investigate the effect of lobeline alone. Samples from 140–240 min were analysed in order to investigate influence of lobeline on the responses to nicotine. If the global analysis indicated an effect of treatment, *post hoc* two level analyses of variance were used to evaluate the statistical significance of the responses to the individual doses of lobeline.

Results

The effect of lobeline administered 10 min prior to a nicotine challenge

In this experiment, the rats were challenged with nicotine (0.4 mg kg^{-1}, s.c.) 10 min after injections of saline or lobeline (0.7, 4.0 or 10.0 mg kg^{-1}, i.p.). Global analysis of the data revealed a significant (F lobeline × time (24,104) = 5.16, $P<0.01$) interaction between the injection of saline or lobeline with time. Further analysis of the data revealed that, in the animals which had received lobeline at doses of 4.0 and 10.0 mg kg^{-1}, i.p. 10 min before a challenge dose of nicotine, the DA overflow in the NAc was significantly (F lobeline (4.0 mg kg^{-1}) × time (8,48) = 3.95, $P<0.05$; F lobeline (10.0 mg kg^{-1}) × time (8,48) = 6.54, $P<0.001$) less than that seen in the saline-treated group (Figure 1a). However, the DA overflow, in the animals which had received 0.7 mg kg^{-1} lobeline, was not significantly different from that seen in the saline-treated animals. The extracellular concentrations of DOPAC in the NAc of these animals is shown in Figure 1b. There was a tendency for DOPAC overflow to be reduced in the groups which had received the two highest doses of lobeline compared with saline-treated animals. However, this effect did not reach statistical significance. Exposure to lobeline 10 min prior to the challenge dose of nicotine caused a significant (F lobeline × time (24,104) = 3.09, $P<0.001$) reduction of the locomotor stimulant response to nicotine. Further analysis suggested that this is due to attenuation of the locomotor stimulation seen in response to nicotine in all three groups of animals given lobeline 10 min before the challenge dose of nicotine and that this occurred to a similar extent, irrespective of the dose of lobeline used (F(8,56) = 3.11, $P<0.001$; F(8,48) = 3.55, $P<0.001$ and F(8,48) = 2.84, $P<0.05$ for 0.7, 4.0 and 10.0 mg kg^{-1}, i.p. respectively) when compared with the saline-treated group (Figure 1c).

The effect of lobeline administered 60 min prior to a nicotine challenge

In comparison with the saline treated rats, there were no significant changes in the extracellular concentrations of DA or DOPAC which could be attributed to the intraperitoneal administration of lobeline at any of the doses tested during the 60 min following these treatments (Figure 2a, time points 20–120 min). There was also no evidence that lobeline elicited locomotor stimulation in these animals. The prior administration of lobeline, 60 min before a nicotine challenge, did not significantly influence the nicotine-induced increase in DA overflow in the nucleus accumbens. However, the administration of lobeline had a significant (F (3,13) = 4.87, $P<0.05$) influence on the DOPAC levels measured following a nicotine challenge 60 min after the lobeline. Analysis of this data revealed that the DOPAC overflow, in response to nicotine, was significantly (F 10.0 (1,7) = 9.43, $P<0.05$) suppressed in the animals which had received 10.0 mg kg^{-1} lobeline in comparison to the animals which had received saline 60 min

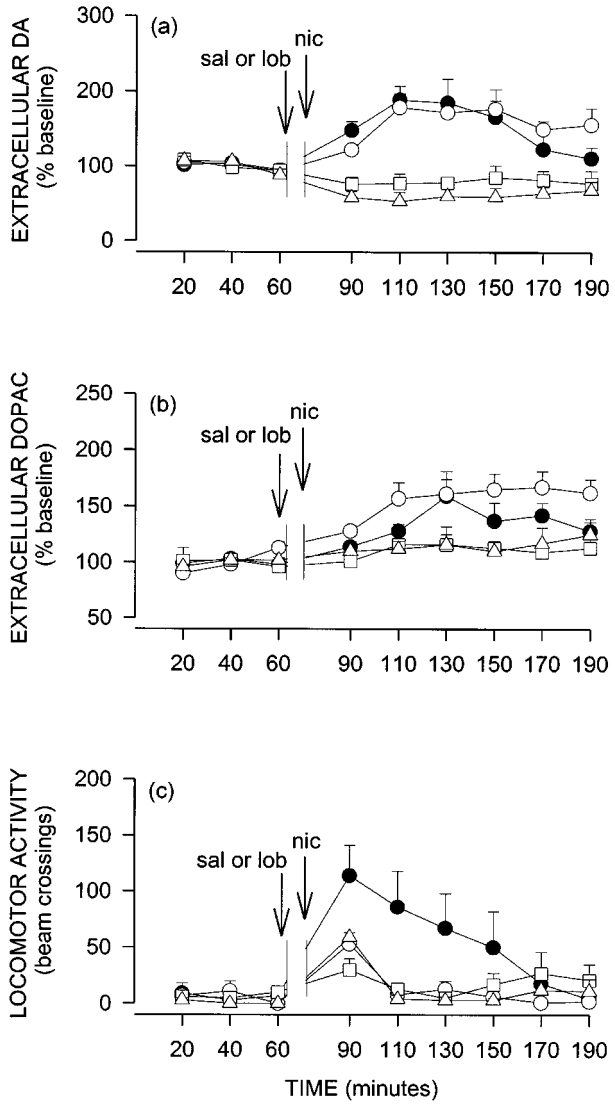

Figure 1 The effect of nicotine administered 10 min after saline or lobeline. All rats were pretreated with daily injections of nicotine (0.4 mg kg^{-1}, s.c.) for 5 days. On day 6, the rats received either saline (●, $n=5$) or lobeline (○, 0.7 mg kg^{-1}, i.p., $n=4$; □, 4.0 mg kg^{-1}, i.p., $n=4$; △, 10.0 mg kg^{-1}, i.p., $n=4$) at the time indicated by the first arrow. All animals received an injection of nicotine (0.4 mg kg^{-1}, s.c.), 10 min later, at the time indicated by the second arrow. The results in panels (a) and (b) are the extracellular levels of DA and DOPAC respectively, expressed as percentages of the means ± s.e.mean of the three samples taken before the injection of saline or lobeline. The results in panel (c) are the means ± s.e.mean of the locomotor activity in these animals. Basal levels of DA and DOPAC, for the animals as a whole before injections of saline or lobeline, were 0.119 ± 0.013 and 14.60 ± 1.48 pmoles 20 μl^{-1} respectively uncorrected for recovery from probe.

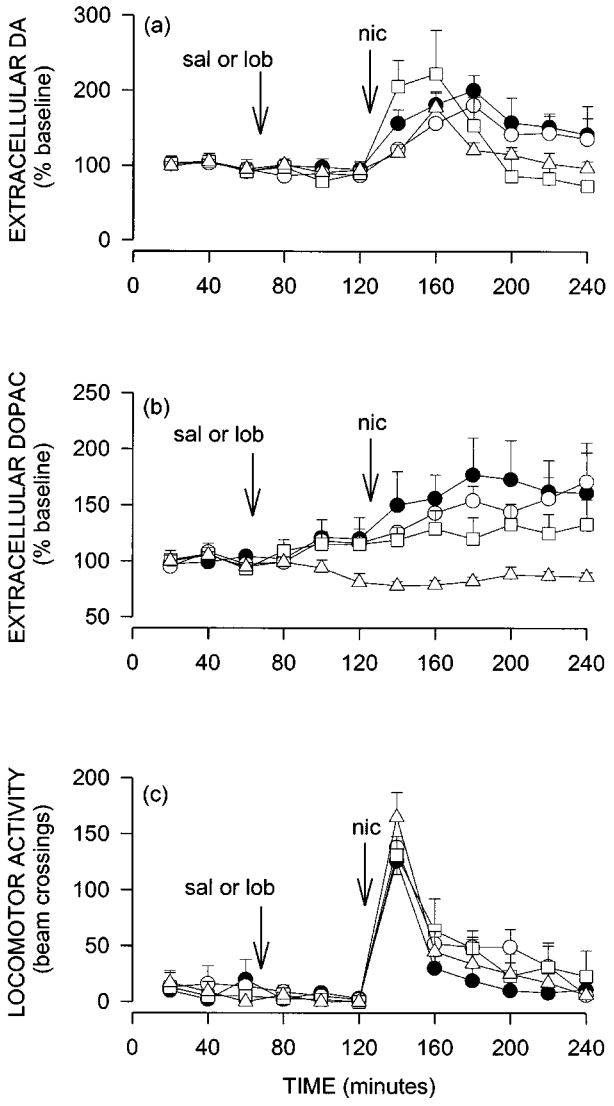

Figure 2 The effect of nicotine administered 60 min after saline or lobeline. All rats were pretreated with daily injections of nicotine (0.4 mg kg^{-1}, s.c.) for 5 days. On day 6, the rats received either saline (●, $n=5$) or lobeline (○, 0.7 mg kg^{-1}, i.p., $n=4$; □, 4.0 mg kg^{-1}, i.p., $n=4$; △, 10.0 mg kg^{-1}, i.p., $n=4$) at the time indicated by the first arrow. All animals received an injection of nicotine (0.4 mg kg^{-1}, s.c.), 60 min later, at the time indicated by the second arrow. The results in panels (a) and (b) are the extracellular levels of DA and DOPAC respectively, expressed as percentages of the means ± s.e.mean of the three samples taken before the injection of saline or lobeline. The results in panel (c) are the means ± s.e.mean of the locomotor activity in these animals. Basal levels of DA and DOPAC, for the animals as a whole before injections of saline or lobeline, were 0.120 ± 0.009 and 13.81 ± 1.44 pmoles 20 μl^{-1} respectively uncorrected for recovery from probe.

prior to the nicotine challenge (Figure 2b). Exposure to lobeline 60 min prior to the challenge dose had no influence on the nicotine-evoked locomotor responses (Figure 2c).

Discussion

Brain DA systems play a role in many of the psychopharmacological responses to nicotine including reinforcement, drug discrimination and locomotion (see Balfour & Benwell, 1993 for review). Decker *et al.* (1995) have proposed that the inability of lobeline to produce reinforcing effects (Fudala & Iwamoto, 1986), generalize to nicotine as a discriminative stimulus (Reavill *et al.*, 1990; Brioni *et al.*, 1993) or stimulate locomotion (Stolerman *et al.*, 1995) may be due to failure of lobeline to stimulate brain DA secretion. The data presented in this study provides evidence to support this hypothesis.

Previous studies in our laboratory have shown that the locomotor stimulant effects of nicotine and its modest effects on DA overflow in the core of the NAc are enhanced in rats which have been pretreated with the drug prior to the test day (Benwell & Balfour, 1992; Birrell & Balfour, 1998). Therefore, in the present study all rats were pretreated with nicotine in order to enhance the putative responses to lobeline and to be

able to investigate the influence of lobeline upon nicotine-elicited responses. The data from the results of the experiment in which lobeline was administered 60 min before a challenge dose of nicotine showed that it did not stimulate DA overflow in the NAc. In addition, lobeline did not stimulate locomotor activity in these rats. Thus, it would appear that lobeline does not act as an agonist at the receptors which mediate the effects of nicotine on these responses.

A prior injection of lobeline 10 min before a challenge dose of nicotine, however, attenuated both the locomotor and DA responses to nicotine, results which suggest that lobeline antagonizes the stimulant effects of nicotine at the neuronal nicotinic AChRs which mediate these responses to nicotine. This appears to be a relatively short term blockade since the DA response to nicotine are similar to controls if the nicotine challenge occurs 60 min after lobeline although the increase in DOPAC overflow, evoked by nicotine, remained attenuated in animals which received the highest dose of lobeline. The reason for this remains unclear although the results suggest that this high dose of lobeline may suppress the increase in DA turnover, evoked by nicotine, for a period which is more prolonged than its effects on DA overflow. Since the effects of lobeline on DA overflow and locomotor activity are of short duration, it is, perhaps, surprising that an injection of lobeline 10 min prior to the nicotine injection abolishes rather than delays the responses to nicotine. In this context, however, it is important to remember that the effects of nicotinic agonists at neuronal AChRs are complex and can involve both stimulation and desensitization of the receptors located on meso-accumbens DA neurones (Benwell *et al*., 1995; Pidoplichko *et al*., 1997). Thus, the responses to nicotine in these circumstances are difficult to predict with certainty.

In agreement with Stolerman *et al*. (1995) and Brioni *et al*. (1993), lobeline failed to elicit a locomotor stimulant effect in the present study. Moreover, the nicotine-evoked locomotion was significantly attenuated when the challenge occurred 10 but not 60 min after lobeline. The inhibition of nicotine-induced locomotion appeared to be maximal at the lowest dose of lobeline tested. It is unlikely that the attenuation is simply due to unmasking of the lobeline-evoked locomotor depressant effect described by Stolerman *et al*. (1995) since, in the latter study, lobeline did not depress activity at doses which bracket the 0.7 mg kg^{-1} used in the present study, a dose which produced maximum inhibition of nicotine-induced locomotor stimulation. Therefore, the attenuation of the nicotine-elicited locomotion is more likely to be due to specific inhibition of the response to nicotine.

Although lobeline is an agonist at some nicotinic AChRs (Jaramilo & Volle, 1968; Nooney *et al*., 1992), the data reported here imply that it has the properties of an antagonist at the nicotinic AChRs which mediate the effects of nicotine on locomotor activity and DA overflow in the nucleus accumbens. The ability of lobeline to act as an antagonist rather than an agonist at nicotinic AChRs has previously been reported for the receptors located on the neuromuscular junction (Lambert *et al*., 1983). The lack of DA release in the NAc in response to lobeline would appear to contrast to the study of Clarke and Reuben (1996) which showed that the compound can stimulate DA release from striatal slices. However, the latter study was carried out *in vitro* with concentrations of lobeline almost certainly greater than those which would be achieved following the systemic administration of lobeline even at the highest dose used in the present study. Moreover, the authors suggested that the lobeline-induced DA secretion was mediated by effects on the DA transporter rather than an action on nicotinic receptors since it was not mecamylamine-sensitive. The present findings are supported by report that lobeline attenuates the increase in DA release from striatal slices evoked by nicotine (JP Sullivan, unpublished observations reported by Decker *et al*., 1995) and antagonizes the effects of nicotine in a behavioural vigilance task (Turchi *et al*., 1995). In addition, Stolerman and colleagues (1995) have suggested that lobeline may exert some of its nicotine-like effects in the brain by acting at non-nicotinic AChRs or, at least, nicotinic AChRs which are insensitive to mecamylamine.

The mechanism, by which lobeline blocks the effects of nicotine at central nicotinic AChRs, remains to be elucidated. Lobeline competes with nicotine at the receptors which bind [^{3}H]-nicotine with high affinity (Reavill *et al*., 1988; Anderson & Arneric, 1994; Damaj *et al*., 1997). Therefore, it is possible that it acts as an antagonist. However, nicotine has been shown to desensitize the neuronal nicotinic AChRs which mediate the effects of nicotine on mesolimbic DA neurones and locomotor activity (Benwell *et al*., 1995; Pidoplichko *et al*., 1997). It is, therefore, perhaps more likely that lobeline causes a rapid and short-lived desensitization of the receptors rather than acting as a simple antagonist.

In the experiments in which lobeline was given 10 min before an injection of nicotine, all three of the dose of lobeline tested blocked the effects of nicotine on locomotor activity whereas only the two higher doses tested (4 and 10 mg kg^{-1}) blocked the effects of nicotine on DA overflow in the accumbens. The reasons for this remain to be established. However, other studies in our laboratory suggest that there is a dissociation between the effects of nicotine on locomotor activity and its effects on DA overflow in the area of the accumbens investigated in this study (Shoaib *et al*., 1994; Balfour *et al*., 1996; Benwell *et al*., 1996). Nicotine exerts its effects in the brain by acting at a family of neuronal nicotinic AChRs (Patrick *et al*., 1993). Therefore, it seems reasonable to suggest that these responses may also be mediated by different isoforms of the neuronal nicotinic AChR and that lobeline preferentially blocks the isoform which mediates the increase in locomotor activity when given at the lowest dose tested in these experiments.

In conclusion, the present study has revealed not only that lobeline fails to stimulate the mesolimbic DA system and locomotion in the rat in a nicotine-like way, but that it exerts a short-lived antagonism of the stimulant effects of nicotine on these responses. The finding that low doses of lobeline selectively and maximally attenuate nicotine-evoked locomotor stimulation but not nicotine-induced increases in DA overflow in the NAc while higher doses inhibit both of these nicotine-evoked responses, suggests that these responses to nicotine may be mediated by different isoforms of the neuronal nicotinic AChR and that lobeline antagonizes these receptors differentially. In addition, the data suggest that the putative beneficial therapeutic properties of lobeline, in smoking cessation (Nunn-Thompson & Simon, 1989; Olin *et al*., 1995) or as a cognitive enhancer (Decker *et al*., 1993) may be achieved with a compound which has little abuse liability.

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References

ANDERSON, D.J. & ARNERIC, S.P. (1994). Nicotinic receptor binding of [^{3}H]cytisine, [^{3}H]nicotine and [^{3}H]methylcarbamylcholine in rat brain. *Eur. J. Pharmacol.,* **253,** 261 – 267.

BALFOUR, D.J.K. & BENWELL, M.E.M. (1993). The role of brain dopamine systems in the psychopharmacological responses to nicotine. *Asian Pacific J. Pharmacol.,* **8,** 153 – 167.

BALFOUR, D.J.K., BENWELL, M.E.M. & BIRRELL, C.E. (1997). Sensitisation of the mesoaccumbens dopamine response to nicotine. *Pharmacol. Biochem Behav.,* **59,** 1021 – 1030.

BALFOUR, D.J.K, BIRRELL, C.E., MORAN, R.J. & BENWELL, M.E.M. (1996). Effects of acute D-CPPene on mesoaccumbens dopamine responses to nicotine in the rat. *Eur. J. Pharmacol.,* **316,** 153 – 156.

BENWELL, M.E.M. & BALFOUR, D.J.K. (1992). The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. *Br. J. Pharmacol.,* **105,** 849 – 856.

BENWELL, M.E.M., BALFOUR, D.J.K. & BIRRELL, C.E. (1995). Desensitisation of the nicotine-induced mesolimbic dopamine responses during constant infusion with nicotine. *Br. J. Pharmacol.,* **114,** 454 – 460.

BENWELL, M.E.M., BALFOUR, D.J.K. & LUCCHI, H.M. (1993). Influence of tetrodotoxin and calcium on changes in extracellular dopamine levels evoked by systemic nicotine. *Psychopharmacology,* **112,** 467 – 474.

BENWELL, M.E.M., HOLTOM, P.E., MORAN, R.J & BALFOUR, D.J.K. (1996). Neurochemical and behavioural interactions between ibogaine and nicotine in the rat. *Br. J. Pharmacol.,* **117,** 743 – 749.

BIRRELL, C.E. & BALFOUR, D.J.K. (1998). The influence of nicotine pretreatment on mesoaccumbens dopamine overflow and locomotor responses to D-amphetamine, *Psychopharmacology,* in press.

BRIONI, J.D., O'NEILL, A.B., KIM, D.J.B. & DECKER, M.W. (1993). Nicotinic receptor agonists exhibit anxiolytic-like effects on the elevated plus-maze. *Eur. J. Pharmacol.,* **238,** 1 – 8.

CLARKE, P.B.S., FU, D.S., JAKUBOVIC, A & FIBIGER, H.C. (1988). Evidence that mesolimbic activation underlies the locomotor stimulant action of nicotine in rats. *J. Pharmacol. Exp. Ther.,* **246,** 701 – 708.

CLARKE, P.B.S. & PERT, A. (1985). Autoradiographic evidence for nicotinic AChRs on nigrostriatal and mesolimbic dopamine neurones. *Brain Res.,* **348,** 355 – 358.

CLARKE, P.B.S. & REUBEN, M. (1996). Release of [^{3}H]-noradrenaline from rat hippocampal synaptosomes by nicotine; mediation by different nicotinic AChR subtypes from striatal [^{3}H]-dopamine release. *Br. J. Pharmacol.,* **117,** 595 – 606.

CORRIGALL, W.A., COEN, K.M. & ADAMSON, K.L. (1994). Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain Res.,* **653,** 278 – 284.

CORRIGALL, W.A., FRANKLIN, K.B.J., COEN, K.M. & CLARKE, P.B.S. (1992). The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *J. Psychopharmacology.,* **107,** 285 – 289.

DAMAJ, M.I., PATRICK, G.S., CREASEY, K.R. & MARTIN, B.R. (1997). Pharmacology of lobeline, a nicotinic AChR ligand. *J Pharmacol. Exp. Ther.,* **282,** 410 – 419.

DECKER, M.W., BRIONI, J.D., BANNON, A.W. & ARNERIC, S.P. (1995). Diversity of neuronal nicotinic acetylcholine receptors: lessons from behaviour and implications for CNS therapeutics. *Life Sci.,* **56,** 545 – 570.

DECKER, M.W., MAJCHRZAK, M.J. & ARNERIC, S.P. (1993). Effects of lobeline, a nicotinic AChR agonist, on learning and memory. *Pharmacol. Biochem. Behav.,* **45,** 571 – 576.

DONNY, E.C., CAGGIULA, A.R., KNOPF, S. & BROWN, C. (1995). Nicotine self-administration in rats. *Psychopharmacology,* **122,** 390 – 394.

FUDALA, P.J. & IWAMOTO, E.T. (1986). Further studies on nicotine-induced conditioned place preference in the rat. *Pharmacol. Biochem. Behav.,* **25,** 1041 – 1049.

HARMANN, S.R. & MARTIN, W.R. (1994). Hyperalgesic and analgesic actions of morphine, U50-488, naltrexone and (−)lobeline in the rat brainstem. *Pharmacol. Biochem. Behav.,* **47,** 197 – 201.

HEIMER, L., ZAHM, D.S., CHURCHILL, L., KALIVAS, P.W. & WOHLTMAN, C. (1991). Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience,* **41,** 89 – 125.

IMPERATO, A., MULAS, A. & DI CHIARA, G. (1986). Nicotine preferentially stimulated dopamine release in the limbic system of freely moving rats. *Eur. J. Pharmacol.,* **132,** 337 – 338.

JARAMILLO, J. & VOLLE, R.L. (1968). A comparison of the ganglionic stimulating and blocking properties of some nicotinic drugs. *Arch Int. Pharmacodyn. Ther.,* **174,** 88 – 97.

LAMBERT, J.J., DURANT, N..N. & HENDERSON, E.G. (1983). Drug-induced modification of ionic conductance at the neuromuscular junction. *Ann. Rev. Pharmacol. Toxicol.,* **23,** 505 – 539.

LENDVAI, B., SERSHEN, H., LAJTHA, A., SANTHA, E., BARANYI, M. & VIZI, E.S. (1996). Differential mechanism involved in the effects of nicotinic agonists DMPP and lobeline to release [^{3}H]-5-HT from rat hippocampal slices. *Neuropharmacology,* **35,** 1769 – 1777.

NISSELL, M., NOMIKOS, G.G. & SWENSSON, T.H. (1994). Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic AChRs in the ventral tegmental area. *Synapse,* **16,** 36 – 44.

NOONEY, J.M., PETERS, J.P. & LAMBERT, J.J. (1992). A patch clamp study of the nicotinic acetylcholine receptor of bovine adreno-medullary chromaffin cells in culture. *J. Physiol.,* **455,** 503 – 527.

NUNN-THOMPSON, C.L. & SIMON, P.A. (1989). Pharmacotherapy for smoking cessation. *Clin. Pharmacol.,* **8,** 710 – 720.

OLIN, B.R., HEBEL, S.K., GREMP, J.L. & HULBERT, M.K. (1995). Smoking deterrents. In *Drug Facts and Comparisons*. eds. Olin, B.R. Hebel, S.K., Gremp, J.L. & Hulbert, M.K. pp. 3087 – 3095. St Louis: J.B. Lippincott Co.

PATRICK, J., SEQUELA, P., VERNIINO, S., AMADOR, M., LUETJE, C. & DANI, J.A. (1993). Functional diversity of neuronal nicotinic acetylcholine receptors. *Prog. Brain Res.,* **98,** 113 – 120.

PAXINOS, G. & WATSON, C. (1986). The rat brain in stereotaxic co-ordinates. 2nd edn. Academic Press, Sydney.

PIDOPLICHKO, V.I., DE BIAS, M., WILLIAMS, J.T. & DANI, J.A. (1997). Nicotine activates and desensitises midbrain dopamine neurones. *Nature,* **390,** 401 – 404.

REAVILL, C., JENNER, P., KUMAR, R. & STOLERMAN, I.P. (1988). High affinity binding of [^{3}H]-nicotine to rat brain membranes and its inhibition by analogues of nicotine. *Neuropharmacology,* **27,** 235 – 241.

REAVILL, C., WALTHER, B. STOLERMAN, I.P. & TESTA, B. (1990). Behavioural and pharmacokinetic studies on nicotine, cytisine and lobeline. *Neuropharmacology,* **29,** 619 – 624.

ROCHFORD, J., SEN, A.P. & QUIRION, R. (1996). Effect of nicotine and nicotinic AChR agonists on latent inhibition in the rat. *J. Pharmacol. Expt. Ther.,* **277,** 1267 – 1275.

SERSHEN, H., BALLA, A,, LAJTHA, A. & VIZI, E.S. (1997). Characterisation of nicotinic AChRs involved in the release of noradrenaline from the hippocampus. *Neurosci.,* **77,** 121 – 130.

SHOAIB, M., BENWELL, M.E.M., AKBAR, M.T., STOLERMAN, I.P. & BALFOUR, D.J.K. (1994). Behavioural and neurochemical adaptations to nicotine in rats: influence of NMDA antagonists. *Br. J. Pharmacol.,* **111,** 1073 – 1080.

SINGER, G., WALLACE, M & HALL, R. (1982). The effects of dopaminergic nucleus accumbens lesions on the acquisition of schedule-induced self-injection of nicotine in the rat. *Pharmacol. Biochem. Behav.,* **17,** 579 – 581.

STOLERMAN, I.P., GARCHA, H.S. & MIRZA, N.R. (1995). Dissociations between the locomotor stimulant and depressant effects of nicotinic agonists in rats. *Psychopharmacology,* **117,** 430 – 437.

STOLERMAN, I.P. & REAVILL, C. (1989). Primary cholinergic and direct dopaminergic mediation of behavioural effects of nicotine. *Prog. Brain Res.,* **79,** 227 – 237.

TENG, L., CROOKS, P.A., SONSALLA, P.K. & DWOSKIN, L.P. (1997). Lobeline and nicotine evoke [^{3}H]overflow from rat striatal slices preloaded with [^{3}H]-dopamine: Differential inhibition of synaptosomal and vesicular [^{3}H]-dopamine uptake. *J. Pharmacol. Exp. Ther.,* **280,** 1432 – 1444.

TURCHI, J., HOLLEY, L.A. & SARTER, M. (1995). Effects of nicotinic acetylcholine receptor ligands on behavioural vigilance in rats. *Psychopharmacology*. **118,** 195 – 205.

VALE, A.L. & BALFOUR, D.J.K. (1989). Aversive environmental stimuli as a factor in the psychostimulant response to nicotine. *Pharmacol. Biochem. Behav.,* **32,** 857 – 860.

VEZINA, P., HERVE, D., GLOWINSKI, J. & TASSIN, J.P. (1994). Injections of 6-hydroxydopamine into the ventral tegmental area destroy mesolimbic dopamine neurons but spare the locomotor activating effects of nicotine in the rat. *Neurosci. Lett.,* **168,** 111 – 114.

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