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Role of dopamine in the behavioural actions of nicotine related to addiction

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Abstract

Experimental impairment of dopamine function by 6-hydroxydopamine lesions or by dopamine receptor antagonists shows that dopamine is involved in nicotine's discriminative stimulus properties, nicotine-induced facilitation of intracranial self-stimulation, intravenous nicotine self-administration, nicotine conditioned place-preference and nicotine-induced disruption of latent inhibition. Therefore, nicotine depends on dopamine for those behavioural effects that are most relevant for its reinforcing properties and are likely to be the basis of the abuse liability of tobacco smoke. On the other hand, in vivo monitoring studies show that nicotine stimulates dopamine transmission in specific brain areas and in particular, in the shell of the nucleus accumbens and in areas of the extended amygdala. These effects of nicotine resemble those of a reward like food except that nicotine-induced release of dopamine does not undergo single-trial, long-lasting habituation. It is speculated that repeated non-habituating stimulation of dopamine release by nicotine in the nucleus accumbens shell abnormally facilitates associative stimulus-reward learning. Acute effects of nicotine on dopamine transmission undergo acute and chronic tolerance; with repeated, discontinuous exposure, sensitization of nicotine-induced stimulation of dopamine release in the nucleus accumbens core takes place while the response in the shell is reduced. It is speculated that these adaptive changes are the substrate of a switch from abnormal incentive responding controlled by consequences (action-outcome responding) into abnormal habit responding, triggered by conditional stimuli and automatically driven by action schemata relatively independent from nicotine reward. These two modalities might coexist, being utilized alternatively in relation to the availability of tobacco. Unavailability of tobacco disrupts the automatic, implicit modality of abnormal habit responding switching responding into the explicit, conscious modality of incentive drug-seeking and craving.

Keywords: Addiction; Dependence; Dopamine; Nicotine; Nucleus accumbens; Prefrontal cortex

1. Introduction

Nicotine exerts behavioural effects in animals and man related to its actions as a behavioural stimulus. These behavioural stimulus properties of nicotine can be distinguished into discriminative, whereby nicotine is utilized to select responses motivated by stimuli and outcomes different from nicotine itself, and motivational, where nicotine is itself the motive of behaviour. Depending on the condition and previous exposure to the drug, nicotine can act as a primary reward or as a punisher. Among brain neurotransmitters, dopamine is by far the one, if not the only, to have been implicated in the behavioural stimulus effects of nicotine. In this short review, I will summarize the experimental evidence, obtained by pharmacological manipulations or lesions of dopamine function, and the correlative evidence, obtained by monitoring changes in dopamine function in behaving subjects administered with nicotine, that bears a relationship with the role of dopamine in the behavioural stimulus properties of nicotine. Existing hypotheses on how this behavioural role of dopamine can be translated into a role in the addictive properties of nicotine will be also discussed.

2. Terminology

In the present review, we will utilize the terms dependence and addiction as defined previously (Di Chiara, 2000). Thus, dependence will be utilized in a broad sense

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to indicate a generic condition of abnormal control exerted by the drug over the subject's behaviour including a milder condition like drug abuse and a severe condition like addiction. Addiction in turn, in agreement with O'Brien (1996) is operationally defined according to DSM-IIIR and DSM-IV criteria for dependence (American Psychiatic Association, 1987, 1994). Therefore, the term dependence, as defined by DSM-III and IV, is replaced by that of addiction and is applied to any condition of drug-seeking that interferes with normal activities and results in drug-related problems. Besides this generic use of the term dependence, we maintain a more specific use to indicate conditions like physiological, physical and motivational dependence.

Throughout this review, we will distinguish two types of appetitive, positive reinforcing stimuli: rewards (primary, either innate or acquired very early in life), and incentives (secondary, conditioned stimuli acquired by learning of their predictive association with rewards). Although this terminology might seem out-dated, we have selected it on purpose as the most appropriate to describe the motivational response properties of dopamine in the nucleus accumbens shell. In fact, dopamine transmission in the shell responds to unpredicted rewards, but not to incentives, thus allowing a clear-cut distinction between these stimuli (see Section 9).

3. Discriminative stimulus effects

Discriminative stimulus effects of nicotine are demonstrated by training subjects to explicitly associate the drug effect to a specific response (e.g., pressing one specific lever among two) that leads to reinforcement (e.g., food presentation). Nicotine allows discrimination between the reinforced and the non-reinforced response. These effects have been reviewed by Stolerman (1987), Rosecrans (1989) and more recently by Stolerman (1999) and by Di Chiara (2000).

Discriminative stimulus properties of nicotine are attributed an important role in tobacco dependence/addiction serving as conditional cues for responding in smoking behaviour; moreover, it is traditionally thought that discriminative stimulus properties of a drug are the expression of its subjective effects (Preston and Bigelow, 1991; Stolerman, 1992; see also Di Chiara, 2000 for a discussion of more recent findings in animals and humans).

In rats trained with 0.1–0.4 mg/kg, nicotine generalizes to the nicotine cue with ED_{50} of 0.036 and 0.14 mg/kg s.c.; smokers can discriminate from saline as little as 2 μg of nicotine given by nasal spray (Perkins et al., 1994a–e).

Evidence for a role of stimulation of dopamine transmission in the discriminative stimulus effects of nicotine comes from studies showing that in rats trained to discriminate nicotine from saline various psychostimulants that have in common the ability of blocking the dopamine carrier such as amphetamine, cocaine and cathinone as well as direct dopamine receptor agonists as apomorphine, a generic dopamine receptor agonist, and SKF82958, a dopamine D1 receptor agonist, mimick the nicotine cue since they elicit responding on the nicotine lever after systemic administration (Chance et al., 1977; Stolerman et al., 1984; Schechter and Meehan, 1993; Mansbach et al., 1998; Gasior et al., 1999). This property extends to agonists of nicotinic receptors other than nicotine; thus, (+) amphetamine showed as much as 75% drug-appropriate responding in rats trained either on nicotine or on cytisine, suggesting that the discriminative stimulus of nicotine mimicked by amphetamine is fully shared by cytisine; cytisine, however, only partially generalized (50%) to the nicotine cue, while nicotine fully generalized to the cytisine cue (Chandler and Stolerman, 1997). Therefore, cytisine seems to reproduce specifically the dopamine-like component of the nicotine discriminative stimulus.

In animals trained to discriminate amphetamine, cocaine or cathinone from saline, nicotine generalizes (although partially in some studies) to the nicotine cue (Ando and Yanagita, 1978; de la Garza and Johanson, 1983, 1985; Reavill and Stolerman, 1987; Schechter and Meehan, 1993; Bardo et al., 1997). Therefore, nicotine and psychostimulants generalize in a partially symmetric fashion to each other's cue, suggesting that they share a common substrate.

Psychostimulants, however, are known to also block the noradrenaline and the 5-hydroxytryptamine reuptake carriers and nicotine does release noradrenaline as well as 5-hydroxytryptamine in brain. Evidence for a role of dopamine rather than noradrenaline and 5-hydroxytryptamine in the discriminative stimulus properties of nicotine comes from the observation that the specific dopamine reuptake blocker GBR12909 at doses of 10–13 mg/kg maximally generalizes to the nicotine cue by 50% in rats trained on 0.4 mg/kg nicotine and by as much as 80% in rats trained on 0.1 mg/kg nicotine (Gasior et al., 1999). Previous negative results by Corrigall and Coen (1994a,b) have been attributed to doses either too low or too high and therefore at the bottom of the bell-shaped dose–response curve of GBR12909 (Gasior et al., 1999).

Further evidence for a role of dopamine in the discriminative stimulus effects of nicotine derives from the observation that dopamine receptor antagonists active on D2 receptors, as haloperidol and spiperone, and on D1 receptors, as SCH23390, reduce nicotine discrimination (Reavill and Stolerman, 1987; Corrigall and Coen, 1994a,b). Indeed, a specific role of dopamine D1 receptors in nicotine discriminative stimulus is suggested also by the high degree (80%) of maximal generalization to the nicotine cue by the relatively specific D1 agonist SKF82958 (Gasior et al., 1999) and is consistent also with inhibition by clozapine (Brioni et al., 1994) and by CGS10746B (Schechter and Meehan, 1992; Gasior et al., 1999), a drug labelled as

a dopamine-release inhibitor, but more likely an atypical dopamine-receptor antagonist (see Di Chiara, 2000 for discussion).

Although clozapine has relatively high affinity for D4 dopamine receptors, a contribution of these receptors to nicotine discriminative stimulus is excluded by the inactivity of the more selective D4 antagonist U101,387 (Mansbach et al., 1998).

Doubts have been raised on the specificity of the generalization to the nicotine cue by dopamine-receptor agonists as well as of the reduction of nicotine discrimination by dopamine-receptor antagonists on the basis of the argument that these effects are associated to a reduction in response rate (Corrigall and Coen, 1994a,b). This argument, in turn, has been utilized to de-emphasize a role of dopamine in the discriminative stimulus effects of nicotine (Corrigall and Coen, 1994a,b).

This conclusion, however, can be disputed on the following grounds: first, amphetamine, cocaine, GBR12909 and SKF82958 have been shown to generalize to the nicotine cue also at doses that do not reduce responding (Gasior et al., 1999); second, nicotine discrimination should be relatively independent from absolute response rates if expressed as percentage of nicotine-appropriate responding.

Therefore, the available evidence indicates that dopamine contributes in a discrete, but distinct fashion to the nicotine cue, at least in rats. Studies on the role of dopamine in nicotine discriminative stimulus in humans, are notable for their absence. Interestingly, however, cocaine users refer on cocaine-like effects elicited by intravenous nicotine (Henningfield and Goldberg, 1983a,b).

4. Motivational stimulus effects

No evidence does exist that dopamine is involved in the negative motivational stimulus properties of nicotine (i.e. aversive and punishing effects). Although this negative conclusion cannot be taken as evidence, it is at least consistent with the idea that dopamine is eventually involved in the adaptation to aversive states and stimuli, but not in their mediation (Di Chiara, 1999).

As to the positive motivational effects of nicotine, evidence has been provided for a role of dopamine in the effects of nicotine on intracranial self stimulation, in intravenous nicotine self-administration and in nicotine-induced place-preference.

4.1. Intracranial self-stimulation

Nicotine lowers current threshold for intracranial self-stimulation in the rat (Huston-Lyons and Kornetsky, 1992; Bauco and Wise, 1994; Ivanova and Greenshaw, 1997). This effect is attenuated by pimozide at doses which, however, by themselves increase threshold for intracranial self-stimulation (Huston-Lyons et al., 1993); more recently, Ivanova and Greenshaw (1997) have reported that haloperidol, at doses that do not affect per se intracranial self-stimulation, completely prevent the threshold-lowering effect of nicotine.

Since the threshold-lowering effect of nicotine on intracranial self-stimulation is indicative of a facilitatory influence on intracranial self-stimulation-reward (Bauco and Wise, 1994), these results can be taken to indicate that dopamine is important for the facilitatory effect of nicotine on intracranial self-stimulation-reward.

4.2. Intravenous self-administration

Nicotine is self-administered intravenously by animals and humans under selected conditions that meet current criteria for reinforcement (see Di Chiara, 2000 for a recent review; Corrigall, 1999).

Evidence for a role of dopamine in nicotine self-administration comes from lesion studies of dopamine neurons performed with 6-hydroxydopamine, systemic administration of neuroleptics and intracranial infusion of nicotinic receptor blockers. Singer et al. (1982a) studied the effect of 6-hydroxydopamine lesions of the nucleus accumbens/ventral striatum on the acquisition of nicotine self-administration induced by a scheduled presentation of food pellets (45 mg, one every 60 s) to rats kept on a lean feeding regimen. Lesioned rats did not acquire, in contrast to sham-lesioned ones, self-administration behaviour; however, the specificity of this effect is uncertain due to the fact that rats were allowed only 2 days to recover from 6-hydroxydopamine lesions and no control for non-specific performance impairment was provided. Also problematic is the specificity of the self-administration behaviour obtained by this procedure as an expression of nicotine reinforcement, given the fact that under the same conditions, a variety of other behaviours are adjunctively promoted (e.g., drinking, wheel running, self-administration of other drugs of abuse, etc.) (Falk, 1971; Singer et al, 1982b). However, food restriction is often utilized as a means to facilitate acquisition of drug self-administration (Carroll et al., 1989), including nicotine self-administration (Corrigall and Coen, 1989). This, coupled to the compulsive nature of adjunctive behaviour, to its dependence on dopamine innervations of the nucleus accumbens (Robbins and Koob, 1980) and to the fact that only reinforcing activities are adjunctively expressed, might signify that drug self-administration is homologous to adjunctive behaviour, a hypothesis advocated by Singer et al. (1982b) and entertained also by other authors (Gilbert, 1978; Sanger, 1986). Given these considerations, the uncertain specificity of the lesion-induced impairment rather than the procedure utilized for inducing nicotine self-administration make the study of Singer et al. (1982a) inadequate to

provide evidence for a role of dopamine in nicotine reinforcement. This problem, however, affects also subsequent studies on the effect of 6-hydroxydopamine lesions on nicotine reinforcement.

Corrigall et al. (1992) have studied the effect of 6-hydroxydopamine lesions of the nucleus accumbens/ventral striatum on nicotine self-administration in rats that had already acquired stable rates of responding for the drug. Rats were tested for nicotine self-administration 4–5 days after intra-accumbens 6-hydroxydopamine. Lesioned rats showed a reduction of responding for nicotine, but also for food on a similar schedule of reinforcement. This observation might suggest that the effects of 6-hydroxydopamine lesions on nicotine self-administration are non-specific, being due to a performance effect rather than to an effect on the rewarding properties of nicotine. Corrigall et al. (1992) have offered a number of arguments to exclude this possibility, but this uncertainty remains also in consideration of the fact that other studies have shown that 6-hydroxydopamine lesions of the ventral striatum impair cocaine self-administration, but leave intact responding for food as well as for morphine (Petitt et al., 1984; Caine and Koob, 1994). Differences in the degree of food restriction and in baseline rates of responding for food as well as in degree of lesion [Corrigall et al. (1992) infused 12 μg of 6-hydroxydopamine in rats pretreated with a monoamine-oxidase inhibitor, while Caine and Koob (1994) infused only 4 μg in unpretreated animals] might account for these discrepancies. Further studies are needed to clarify this important issue.

The effect of systemic dopamine-receptor antagonists specific for D1-like (SCH23390) and for D2-like receptors (spiperone) on intravenous nicotine self-administration has been studied in rats by Corrigall and Coen (1991a,b). Dopamine-antagonists induced a dose-related, extinction-like intrasession reduction of responding for nicotine self-administration, suggestive of an impairment of the reinforcing properties of nicotine; only at higher doses SCH23390 impaired responding from the beginning of the session, an effect suggestive of a non-specific performance effect. This effect of dopamine-receptor blockers resembles that observed by Wise (1982) and interpreted by Wise himself in terms of reduction of reward-induced hedonia (anhedonia hypothesis) and, later on, of incentive/activational properties of reinforcers.

More recently, an interpretation of the extinction-like effect of dopamine-receptor antagonists in terms of impairment of associative stimulus-reward learning has been also provided (Di Chiara, 1999).

In the studies by Corrigall and Coen (1991a,b), similarly to those of Wise (1982), dopamine-receptor blockers, at doses that impair responding for nicotine also impair responding for food on an operant schedule identical to that utilized for nicotine and in an extinction-like fashion similar to that observed for nicotine (Corrigall and Coen, 1991a,b).

This observation, again, raises the problem of specificity. However, it is also possible that the general effects on reinforcement observed after experimental manipulations of dopamine transmission are the result of a general involvement of dopamine at different steps in the acquisition, maintenance and expression of rewarded behaviour (see Di Chiara, 1999 for discussion).

That this might be the case is strongly suggested by the observation, again by Corrigall et al. (1994), that intra-tegmental infusion of dihydro-β-erythroidine in the area of origin (but not in the area of termination) of dopamine neurons projecting to the ventral striatum reduces selectively nicotine self-administration as responding for cocaine or food is left intact.

From these observations, one can draw the conclusion that nicotine reinforcement results from an action of nicotine on nicotinic receptors located proximally on dopamine neurons or in their vicinity and activating dopamine transmission in terminal areas of the dopamine mesolimbic system. Thus, nicotine appears to activate an input on dopamine neurons that makes nicotine itself reinforcing.

Recently, Picciotto et al. (1998) have reported that mutant mice lacking the β2 subunit of the nicotinic acetylcholine receptor do not self-administer nicotine and do not show a stimulatory dopamine response to nicotine estimated by in vitro patch-clamp recording of dopamine units in the ventral tegmental area or by in vivo monitoring of extracellular dopamine by microdialysis. Although these results are consistent with a role of dopamine in the reinforcing properties of nicotine, the fact that the β2 subunit is the most diffuse among neuronal nicotinic acetylcholine receptors subunits (Wada et al., 1989) makes this evidence equivalent to that obtained by an antagonist of nicotinic acetylcholine receptors such as dihydro-β-erythroidine that is regarded to preferentially block α4 β2 receptors (Alkondon et al., 1994).

In contrast with the relative variety of studies in animals on the role of dopamine in nicotine reward and reinforcement, no studies made with pure nicotine are available in humans. Therefore, only studies with cigarette smoking can be considered.

The effect of haloperidol on cigarette smoking in humans has been studied both in normal volunteers (Dawe et al., 1995) as well as in schizophrenic patients (McEvoy et al., 1995). These studies are concordant in reporting an increase in nicotine self-administration expressed by blood nicotine (Dawe et al., 1995) and by smoking behaviour (McEvoy et al., 1995) after haloperidol as compared to placebo. In normal smokers, the increase in nicotine intake took place without any reported change in subjective measures of smoking satisfaction or craving. Therefore, there seems to be a difference between humans and rats in the behavioural response to dopamine receptor blockade: compensatory increase in humans, reduction in rats. Differences in the route of administration might be relevant for these differences, as neuroleptics might reduce the stimu-

lus properties of nicotine given intravenously, but not those of smoked nicotine, which might exert peripheral stimulus effects by a direct action on the upper respiratory tract. As pointed out by Rose and Corrigall (1997), parallel studies in men with intravenous nicotine would be useful to clarify this point.

4.3. Conditioned place-preference

Animals, just like humans, prefer and approach environments that have been repeatedly paired to stimuli with positive motivational properties. Drugs of abuse induce preference for that compartment among two that has been repeatedly paired to their effects (conditioned place-preference) (Carr et al., 1989). Experimental conditions can be adjusted to differentiate the two compartments of the apparatus for place-preference not only for their sensory, but also for their motivational properties, thus introducing a preference bias for one compartment over the other. Even in conditions where no bias for a specific compartment is present in the whole subject population, a small individual bias can still be shown (Acquas and Di Chiara, 1994).

Nicotine exerts opposite motivational effects that has made it difficult to demonstrate robust place-preference of the kind shown by other drugs of abuse like morphine and amphetamine. However, in spite of negative results (Clarke and Fibiger, 1987; Parker, 1992) and even reports of conditioned place-aversion (Jorenby et al., 1990), preference has been reported with nicotine at doses of 0.1–0.8 mg/kg under biased (Fudala and Iwamoto, 1986; Fudala et al., 1985; Acquas et al., 1989; Carboni et al., 1989a,b; Calcagnetti and Schechter, 1994) and unbiased conditions (Horan et al., 1997; Dewey et al., 1999; Spina et al., in preparation).

The effect of the dopamine D1 receptor antagonist SCH23390 on the acquisition of nicotine-induced place-preference has been studied under biased (Acquas et al., 1989) and unbiased conditions (Spina et al., in preparation) with fixed pairing of nicotine with the less preferred compartment. Doses of 0.05 mg/kg s.c. of SCH23390 given in both compartments prevented the acquisition of place-preference induced by nicotine (0.6 mg/kg s.c.) under biased conditions (Acquas et al., 1989). SCH39166 (0.012–0.025 mg/kg s.c.), a more selective antagonist of D1 receptors than SCH23390, impairs acquisition of place-preference conditioned by nicotine (0.6 mg/kg s.c.) in unbiased conditions (Spina et al., in preparation).

SCH23390, while preventing acquisition of nicotine-conditioned place-preference, fails to affect its expression, consistent with the idea that dopamine is important for reinforcement and, more specifically, for stimulus-reward learning (Di Chiara, 1999) rather than for expression of incentive-motivation (Horvitz and Ettenberg, 1991; McFarland and Ettenberg, 1995).

5. Locomotion

Nicotine elicits biphasic inhibitory–stimulatory effects on locomotion in a baseline-dependent fashion (see Di Chiara, 2000 for review).

Evidence for a role of dopamine of the mesolimbic system in the locomotor stimulant effects of nicotine derives from three different approaches: 6-hydroxydopamine lesion of dopamine neurons (Clarke et al., 1988a,b; Louis and Clarke, 1998), blockade of dopamine receptors by D1 and D2 receptor antagonists (Walter and Kuschinsky, 1989; Corrigall and Coen, 1991a,b; O'Neill et al., 1991) and blockade of nicotinic receptors in the area of origin of mesolimbic dopamine neurons by local infusion of dihydro-β-erythroidine, a competitive antagonist of nicotinic receptors (Corrigall et al., 1994). These manipulations reduce the locomotor stimulant effects of nicotine.

Consistent with this evidence are the reports of stimulation of locomotion in the rat after local infusion of nicotine (Reavill and Stolerman, 1990; Leikola-Pelho and Jackson, 1992; Nisell et al., 1994a; Panagis et al., 1996) and cytisine (Museo and Wise, 1990b, 1995) in the ventral tegmentum. In spite of the fact that locomotion can be obtained also by infusion of cytisine in the nucleus accumbens (Museo and Wise, 1990a; Wise et al., 1995a,b), intra-accumbens infusion of dihydro-β-erythroidine fails to affect locomotion stimulated by nicotine (Corrigall et al., 1994). Negative results by Vezina et al. (1994) after infusion of the 6-hydroxydopamine into the nucleus accumbens are contradicted by the positive ones of Louis and Clarke (1998).

Issues of specificity can be raised also for the effect of experimental manipulations of dopamine transmission on nicotine-induced hypermotility, as both dopamine receptor blockers and 6-hydroxydopamine lesions can reduce spontaneous locomotion; however, 6-hydroxydopamine lesions of the nucleus accumbens that reduce nicotine locomotion do not affect spontaneous activity (Clarke et al., 1988b). Similar observations have been reported with dopamine-receptor antagonists (O'Neill et al., 1991). These observations are notable in view of the fact that drug-conditioned locomotion (Beninger, 1983), expression of conditioned place-preference, conditioned running in a straight alley (Horvitz and Ettenberg, 1991; McFarland and Ettenberg, 1995) and conditioned reinforcement (Robbins, 1975) are not impaired by dopamine-receptor antagonists nor by 6-hydroxydopamine lesions. This contrasts with the effectiveness of the same experimental manipulations in preventing the facilitation of these responses by agonists or by drugs that release dopamine, including nicotine. It appears therefore that the mechanism by which conditional stimuli elicit behavioural responses is quite different from that by which drugs of abuse elicit behavioural effects. This differential dopamine dependence of drug-induced behavioural effects and conditional non-drug responses has been overlooked by some theorists; as a matter of fact, the dopamine

dependence of drug-induced behaviour has been the basis for implicating dopamine in responding to conditional stimuli and for envisioning it as the substrate of the incentive properties of these stimuli (Wise, 1982; Robinson and Berridge, 1993). However, the similarity between dopamine-dependent behavioural effects of drugs and spontaneous behavioural responses to stimuli is only superficial. On the other hand, mechanisms such as that postulated by Robinson and Berridge (1993), envisioning a phasic role of dopamine released in the nucleus accumbens in response to conditional stimuli, in mediating the incentive-motivational properties of these stimuli, are not supported by direct measurements of dopamine transmission by brain microdialysis following presentation of stimuli conditioned to food or to a self-administered drug (cocaine) (Neisewander et al., 1996; Bassareo and Di Chiara, 1997).

6. Latent inhibition

Latent inhibition (LI) describes the circumstance that pre-exposure to a given stimulus without consequences impairs the ability of the same stimulus to be conditioned by a primary reinforcer (either aversive or rewarding).

Nicotine, like amphetamine, abolishes latent inhibition in rats, an effect reversed by haloperidol (Joseph et al., 1993). In humans, an effect of nicotine on latent inhibition has not been demonstrated (Thornton et al., 1996).

The effect of nicotine takes place during conditioning rather than pre-exposure and this has been interpreted as a reflection of a role of dopamine in switching of associative processing of the motivational representation of the stimulus from the motivationally neutral condition of pre-exposure to the meaningful one of reinforcement (Weiner, 1990). Other explanations, however, have been provided (Killcross et al., 1994a,b).

Whatever the mechanism, the effect of nicotine on latent inhibition adds to the effects of nicotine that are dependent upon an intact dopamine transmission.

7. Dopamine transmission

7.1. Acute effects in nicotine-naive subjects

Nicotine acutely stimulates dopamine transmission after systemic administration in rats naive to nicotine.

The most direct and specific method available for estimating dopamine transmission in vivo is by monitoring endogenous dopamine in the extracellular fluid by microdialysis (Di Chiara 1990; Di Chiara et al., 1996a,b). Nicotine increases dopamine in dialysates at doses of 0.1–0.6 mg/kg s.c. and 0.05 mg/kg i.v. depending on the area where dopamine transmission is monitored. The areas most sensitive to the dopamine-stimulant effect of acute nicotine are the nucleus accumbens shell (Pontieri et al., 1996) and the bed nucleus of the stria terminalis (Carboni et al., 2000a,b), two areas that show homologies related to their link with the so-called ''extended amygdala'' (Heimer et al., 1991) (Fig. 1). Doses of nicotine that are threshold for activation of dopamine transmission in these areas are ineffective in other terminal dopamine areas, namely, dorsal striatum, prefrontal cortex and core of the nucleus accumbens. Some studies have failed to observe a stimulation of dopamine release by nicotine in the nucleus accumbens of rats naive to nicotine (Benwell and Balfour, 1992; Reid et al., 1996), in contrast with most of the literature (see Di Chiara, 2000 for review). According to the same group, repeated exposure to a schedule of nicotine that induces behavioural sensitization makes nicotine effective in stimulating dopamine release in the nucleus accumbens under conditions under which it would be otherwise ineffective in nicotine-naive rats (Benwell and Balfour, 1992). Other authors have reported just the opposite: stimulation of dopamine release by nicotine in the nucleus accumbens of nicotine-naive rats, but no sensitization to nicotine (Nisell et al., 1996).

These contrasting results can be explained as the result of the shell/core heterogeneity in the responsiveness of dopamine transmission in the nucleus accumbens to nicotine coupled to differential changes in the responsiveness of the shell versus core to repeated exposure to the drug. Evidence for this possibility has been recently provided by us (Cadoni and Di Chiara, 2000). Thus, in rats naive to nicotine and repeatedly administered with saline, nicotine (0.4 mg/kg s.c.) increased dialysate dopamine in the shell, but not in the core of the accumbens. In rats given nicotine (0.4 mg/kg s.c.) for 4 days, challenge with the same dose of nicotine resulted in potentiation of its dopamine-stimulant effect in the core and reduction in the shell (Fig. 2). Therefore, repeated exposure to nicotine induces reciprocal changes in the responsiveness of dopamine transmission in the two subdivisions of the nucleus accumbens: sensitization in the core, tolerance in the shell (Cadoni and Di Chiara, 2000). This property of nicotine, in turn is common to other drugs of abuse; thus, exposure to a schedule of morphine, cocaine or amphetamine that induces behavioural sensitization results in reciprocal adaptive changes in drug-responsiveness of dopamine transmission in the shell and in the core of the nucleus accumbens similar to those induced by repeated exposure to nicotine (Cadoni and Di Chiara, 1999, 2000; Cadoni et al., 2000). Although the relationship between these changes and the stimulant actions of nicotine on behaviour is unknown, these observations are consistent with two major properties of the dopamine-stimulant effects of nicotine: their topographic specificity and their similarity with other drugs provided with reinforcing properties and abused by humans. In fact, most drugs of abuse, like nicotine, preferentially stimulate dopamine transmission in the nucleus accumbens of drug-naive rats (Di Chiara and Imperato, 1988), and in particular, in its shell (Pontieri et al., 1995, 1996; Tanda et al., 1997a,b).

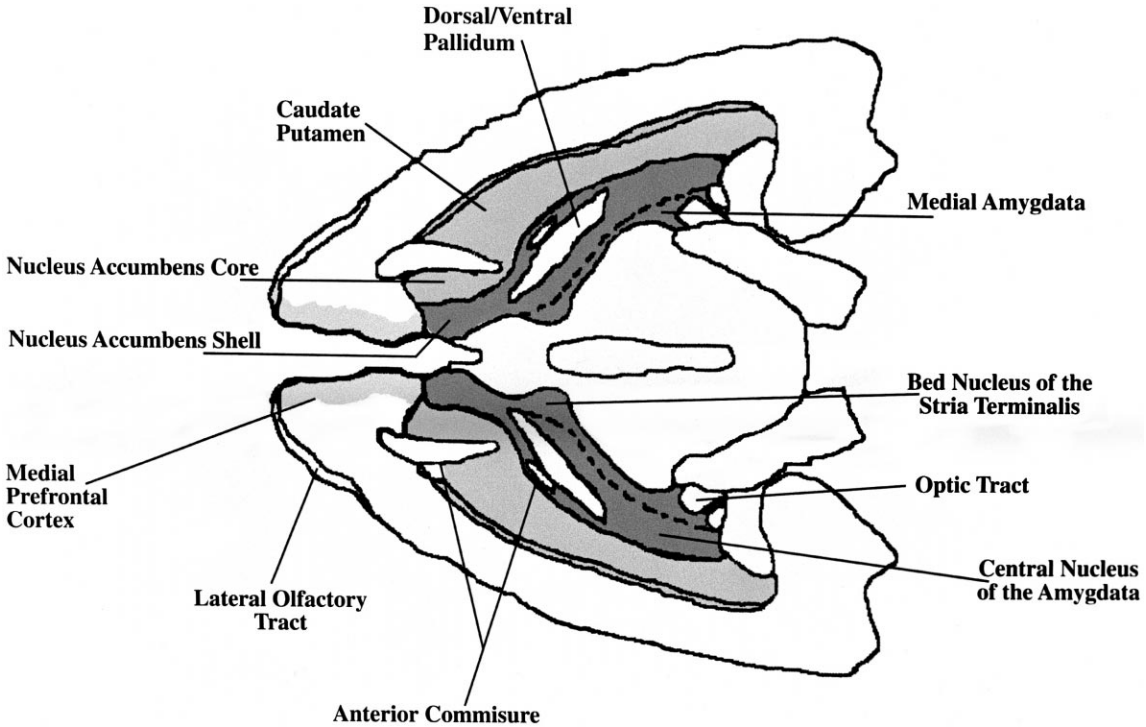

Fig. 1. The striatal complex, nucleus accumbens subdivisions (shell and core) and the extended amygdala. Reproduced with permission from Heimer et al. (1991) with modifications.

7.2. Mechanism of the acute dopamine-stimulant effect of nicotine

The mechanism by which nicotine increases dopamine transmission in the nucleus accumbens is likely to be a complex one. The principal mechanism might be a proximal being related to stimulation of the frequency of spike-generation (firing) in dopamine neurons and to an increase in the proportion of burst-firing. This mode is most efficient for transmitter release and synaptic transmission; dopamine neurons, in contrast to other monoaminergic neurons, possess this modality, indicative of the ability of dopamine transmission to respond not only tonically, but also phasically to stimuli.

Nicotine elicits these changes both in vivo, as shown by extracellular single-unit recording, as well as in vitro, as shown by intracellular recording in mesencephalic slices. Comparative dose-response studies showed A10 neurons to be more sensitive than A9 neurons to the stimulant action of nicotine (Mereu et al., 1987), consistent with the preferential stimulant effects of nicotine in the nucleus accumbens (innervated by A10 neurons) shown by microdialysis studies (Imperato et al., 1986; Pontieri et al., 1996).

In vitro studies have provided evidence on the receptor mechanism by which the effects of nicotine on dopamine neurons could take place. Thus, pressure injection of acetylcholine on ventral tegmental area neurons in vitro showed two components, a fast one, peaking in about 30 ms, and a slower one, peaking in about 50 ms. These two components had different pharmacological properties and resistance to desensitization. Thus, the fast component was sensitive to α-bungarotoxin and methyllicaconitine-bloc-

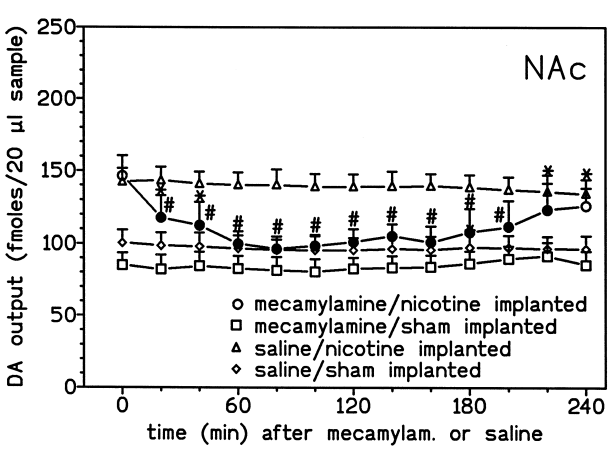

Fig. 2. Effect of chronic infusion of nicotine by osmotic minipumps and of mecamylamine challenge (1 mg/kg s.c.) on dialysate dopamine in the nucleus accumbens shell. Values are means ± SEM of the data obtained in at least six animals expressed in fmol/20 µl sample. Closed symbol: $p < 0.05$ from basal. $^{*}p < 0.05$ from the correspondent value of sham-implanted rats; $\#p < 0.05$ from the correspondent value of saline in nicotine-implanted rats (modified with permission from Carboni et al., 2000a).

kade, but not to mecamylamine blockade and more prone to desensitization than the slower, mecamylamine-sensitive component. These properties have led to the assignment of the fast component to α7-containing nicotinic acetylcholine receptors and of the slow component to an α3/α4 β2 nicotinic acetylcholine receptor (Pidoplichko et al., 1997).

These observations suggest the existence of post-synaptic non-α7 as well as α7-containing nicotinic acetylcholine receptors mediating the acute stimulant effect of nicotine on dopamine neurons of the ventral tegmental area. Indeed, mRNA for most subunits of neuronal nicotinic acetylcholine receptors have been shown to be expressed by dopamine neurons, namely, α2, α3, α4, α5, α6, β2 and β3 subunits (Deneris et al., 1989; Wada et al., 1989, 1990; Dineley-Miller and Patrick, 1992; LeNovere et al., 1996); moreover, an association of β2 (Swanson et al., 1987; Hill et al., 1993), α6 (Goldner et al., 1997) and α4 subunits (Sorenson et al., 1998; Arroyo-Jimenez et al., 1999) with tyrosine-hydroxylase-positive neurons of the substantia nigra and ventral tegmental area has been shown by light and electron microscopic immunohistochemistry; on the other hand, mRNA for α7 subunits has been reported to be expressed by ~50% of dopamine neurons in the rats' substantia nigra and ventral tegmental area (Azam et al., 1999).

Nicotinic receptors might influence the activity of dopamine neurons also in an indirect manner, by promoting release of an excitatory transmitter (glutamate) onto dopamine neurons through an action on presynaptic α7-containing nicotinic receptors. The evidence for this mechanism is indirect: thus, the ability of local intra-tegmental infusion of methyllicaconitine to reduce nicotine-induced release of dopamine in the nucleus accumbens, implicates an α7-containing receptor (Schilström et al, 1998a,b), not necessarily a presynaptic receptor; indeed, the α7 receptors demonstrated to date in relation to dopamine neurons are localized post-synaptically on the dopamine neurons themselves rather than presynaptically on terminals impinging on them (see above and Pidoplichko et al., 1997); similarly, the ability of glutamate antagonists infused in the ventral tegmentum to impair nicotine-induced release of dopamine in the nucleus accumbens is not necessarily indicative of a presynaptic mechanism (Schilström et al., 1998a; Svensson et al., 1998).

Distal mechanisms, related to an action of nicotine in terminal dopamine areas, have also been implicated in the mechanism of the stimulant action of nicotine on dopamine transmission. Two possibilities have been envisioned, a direct presynaptic action of nicotine on dopamine terminals or an indirect action via nicotinic receptors located on terminals impinging on dopamine neurons (see Wonnacott, this volume). Although nicotinic acetylcholine receptors controlling dopamine release have been demonstrated also in synaptosomes from the nucleus accumbens, most studies, for obvious practical reasons, have been performed in whole striatal preparations; instead, in vivo studies have been performed mainly in the nucleus accumbens (if not in its shell subdivision), given the relative insensitivity of neo-striatal (dorsal striatal) dopamine transmission to systemic nicotine; because of this, the relationship between the studies made in striatal in vitro preparations and the in vivo effects of nicotine is obscure; this, in turn, makes it difficult to utilize in vitro dopamine release studies as a basis for explaining the mechanism of the in vivo effects of nicotine on dopamine transmission.

An indirect test of the role of distal mechanisms, however, is offered by studies on the effect of local infusion of nicotinic antagonists on the release of dopamine in the nucleus accumbens after systemic administration of nicotine. In these studies, nicotine effects were impaired by intra-tegmental, but not intra-accumbens mecamylamine (Nisell et al., 1994b). Recently, it has been reported that intra-accumbens α-bungarotoxin, a selective blocker of α7-containing nicotinic acetylcholine receptors, reduces the release of dopamine stimulated by systemic nicotine in this area (Fu et al., 1999a,b). This issue, therefore, awaits clarification.

Among other mechanisms that might contribute to the effects of nicotine on dopamine transmission in vivo, the possibility of an impairment of dopamine-reuptake by nicotine, reported by Izenwasser et al. (1991) in vitro, is unlikely, given the observation that the clearance of dopamine in the nucleus accumbens in vivo is increased rather than decreased by nicotine (Ksir et al., 1995).

In light of the results of studies directly estimating dopamine transmission in vivo by microdialysis, earlier reports of stimulation by nicotine of the synthesis, metabolism and turnover in terminal areas of the mesolimbic system (reviewed by Di Chiara, 2000) can be explained as secondary to stimulation of the exocytotic release of dopamine from the terminals of mesolimbic dopamine neurons.

In conclusion, nicotine acutely stimulates the release of dopamine, estimated by brain microdialysis, specifically in the nucleus accumbens shell/extended amygdala at doses that are well in the range of those self-administered intravenously in rats (around 0.05 mg/kg). At higher doses, dopamine release is increased also in the dorso-lateral caudate–putamen and in the prefrontal cortex.

The main mechanism of these acute effects appears to be the activation of non-α7- as well as α7-containing nicotinic acetylcholine receptors with resulting depolarization of dopamine neurons and firing of action potentials. This primary action might be modulated at the somato-dendritic region by an *N*-methyl-D-aspartate input on dopamine neurons, eventually facilitated by a presynaptic action of nicotine on glutamate terminals (see above), which promotes burst firing. An action of nicotine on presynaptic receptors in the terminal regions of dopamine neurons might further modulate dopamine transmission by affecting the efficiency of stimulus-secretion coupling

rather than by directly releasing dopamine. The notion that the primary action of nicotine on dopamine transmission is mediated by non-α7 nicotinic acetylcholine receptors is indirectly confirmed by the observation of Picciotto et al. (1998) that mutant mice not expressing the β2 subunit of the nicotinic acetylcholine receptor (which is not known to associate with α7 subunits) also do not show a stimulatory dopamine response to nicotine both in vivo, estimated by microdialysis as well as in vitro, by electrophysiology.

7.3. Tolerance and sensitization

Exposure to nicotine elicits changes in the functional responsiveness of nicotinic receptors to the agonist (desensitization, inactivation) that are regarded as the substrate of changes in pharmacological effects generically indicated as tolerance since it consists a decrease in the potency of nicotine in eliciting the same effects. Exposure to nicotine, however, can also result, depending on the experimental conditions, in an apparent increase in drug response (sensitization). The effects of nicotine on dopamine transmission can similarly undergo tolerance or sensitization depending on the schedule of exposure to nicotine. This complex topic has been recently reviewed (Di Chiara, 2000) and will be only summarized here.

Single doses of nicotine induce reversible acute tolerance to nicotine-induced release in the nucleus accumbens that is maximal after 1 h and is lost by 3 h after nicotine (Maisonneuve et al., 1997). This time-course explains the failure of some studies to observe tolerance between doses of nicotine repeated over 24 h (Damsma et al., 1989; Nisell et al., 1996).

Continuous exposure to nicotine for 9 days by administration via subcutaneous osmotic minipumps results in higher than control levels of dopamine in nucleus accumbens dialysates; mecamylamine administration reversibly reduced dopamine levels to control values with a time-course compatible with mecamylamine kinetics (Blackburn et al., 1992; Carboni et al., 2000a) (Fig. 3). These results indicate that, even in the presence of levels of nicotine well above those sufficient to induce full desensitization of nicotinic acetylcholine receptors, chronic exposure to nicotine does not result in complete tolerance to nicotine-induced stimulation of dopamine release in the nucleus

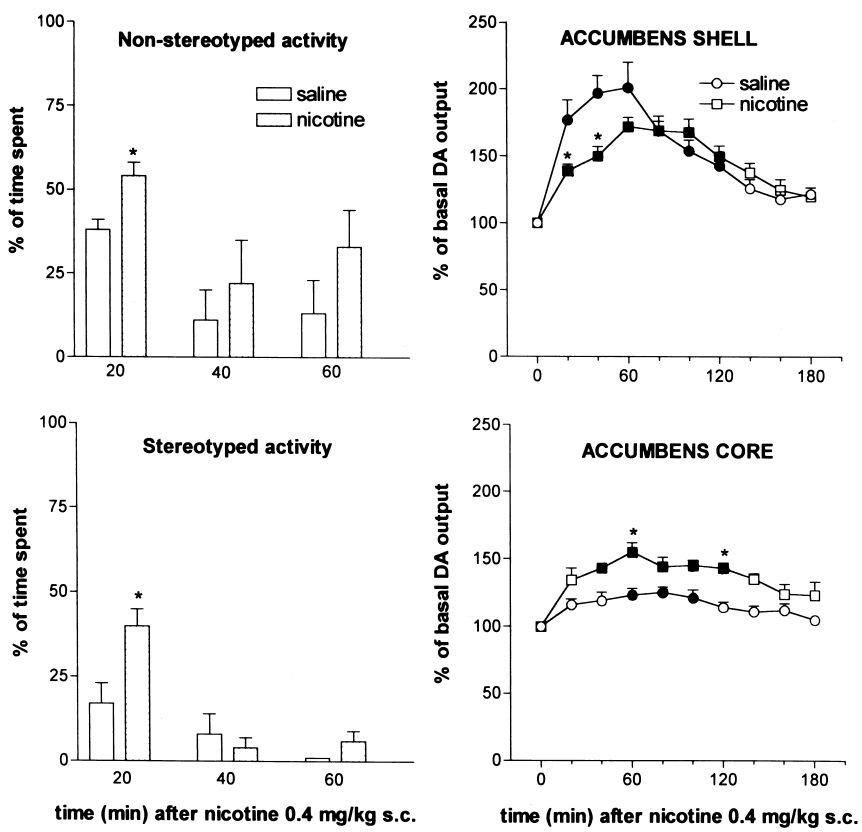

Fig. 3. Behavioral and biochemical effects of nicotine challenge (0.4 mg/kg s.c.) in rats pretreated with saline or nicotine. Left panels show the effect of nicotine on behavior of saline (unfilled bars) and nicotine (hatched bars) pretreated rats. Results are expressed as means ± SEM of the percentage of time spent in each behavioral item. $^{*}p < 0.05$ versus the correspondent value of the control (Student's *t*-test). Right panels show the effect of nicotine on basal dopamine output in dialysates from nucleus accumbens shell and core of saline (circles) and nicotine (squares) pretreated rats. The results (mean ± SEM) are expressed as percentage of basal values. Filled symbols represent points that are significantly different ($p < 0.05$) from respective basal values by two-way ANOVA followed by Tukey's test. $^{*}p < 0.05$ versus the corresponding time point of the control group by two-way ANOVA followed by Tukey's test (modified with permission from Cadoni and Di Chiara, 2000).

accumbens. These results are apparently at variance with those of Hildebrand et al. (1997) who, under similar conditions, did not obtain a significant increase of dialysate dopamine. However, closer examination of the data reveals that dopamine levels were actually increased (61% over control values) not less than in the study of Carboni et al. (2000a) (51% over control values) although not significantly; the smaller size of the sample ($N = 9$) utilized in the study of Hildebrand et al. (1997) compared to that of Carboni et al. (2000a) ($N = 20$) could have made the difference.

Repeated exposure to nicotine by once-a-day administration of 0.4 mg/kg for 5 days results in behavioural sensitization and in sensitization to the dopamine stimulant-effect of nicotine in the nucleus accumbens (Benwell and Balfour, 1992). It will be recalled (see above) that these authors consistently failed to observe stimulation of dopamine release by nicotine in the nucleus accumbens of control rats and that these observations are at variance with most studies showing a stimulation of dopamine release in the nucleus accumbens of nicotine-naive rats. In contrast, Nisell et al. (1996), using a longer lasting (12 days) single daily schedule of nicotine exposure have not observed a sensitization of dopamine release in the nucleus accumbens by microdialysis in freely moving rats, and Nisell et al. (1997a,b) actually obtained tolerance after the same schedule both in the shell and in the core of the nucleus accumbens of rats pretreated with a monoamine-oxidase inhibitor and monitored by voltammetry.

These discrepancies have been explained as due to differences in the adaptive changes induced by repeated nicotine exposure in the two subdivisions of the nucleus accumbens. Thus, repeated nicotine exposure with the same schedule utilized by Benwell and Balfour (1992), results in sensitization in the core and tolerance in the shell (Cadoni and Di Chiara, 2000). An additional factor in this process is probably the duration and the schedule of the exposure to nicotine. Thus, while chronic tolerance is more likely to be induced by continuous and prolonged exposure to nicotine, sensitization is normally induced by intermittent exposure to nicotine. Nonetheless, continuous exposure to nicotine at doses that result in tolerance to nicotine-induced sensitization of dopamine release in the nucleus accumbens, induces itself a sensitization that is expressed as soon as chronic tolerance wears off (Benwell et al., 1995); therefore, tolerance and sensitization of nicotine-induced stimulation of dopamine release in the nucleus accumbens are distinct adaptive changes that compete and require different conditions for expression although they can be induced by the same schedule of nicotine exposure.

7.4. Dependence

The ability of chronic exposure to nicotine to induce dependence of dopamine transmission is debated. Thus, Hildebrand et al. (1997) have recently reported that challenge with mecamylamine of rats implanted with subcutaneous osmotic minipumps delivering about 10.27 mg/kg/day of nicotine tartrate results in a reduction of dopamine in nucleus accumbens dialysates not only in comparison with pre-mecamylamine values, but also with a control group not infused with nicotine. In contrast, Carboni et al. (2000a) observed a reversible reduction of dialysate dopamine in the nucleus accumbens compared to pre-mecamylamine values, but not to saline-infused controls. Failure to observe a reduction of dopamine output after mecamylamine cannot be due to an insufficient degree of dependence or of withdrawal as mecamylamine was effective in precipitating a physical withdrawal syndrome and increased dopamine in the prefrontal cortex (Carboni et al., 2000a); the reason for these discrepancies is unclear.

The negative results obtained by Benwell et al. (1995) upon removal of nicotine minipumps are not significant given the fact that this group also obtained negative results after acute nicotine in naive subjects (see above).

As to other terminal dopamine areas, mecamylamine-precipitated withdrawal has been reported to be associated to reduction of dialysate dopamine in the central amygdala, an area included in the extended amygdala (Svensson et al., 1998) and in the prefrontal cortex (Carboni et al., 2000a). As nicotine does not reduce dopamine release in the prefrontal cortex in naive subjects, and in view of the particular sensitivity of dopamine transmission in the prefrontal cortex to motivational stimuli, including aversive one (Di Chiara et al., 1999), these changes should be viewed as the result of the motivational aversive state of abstinence rather than of a dependence state of mesocortical dopamine neurons after chronic nicotine exposure.

8. Commonalities between nicotine and other dependence-producing drugs

Nicotine shares with non-psychostimulant drugs as narcotic analgesics, delta-9-tetrahydrocannabinol and ethanol the ability of stimulating dopamine transmission preferentially in the shell of the nucleus accumbens by activating dopamine neurons that project to this area (Di Chiara, 1995, 1998, 1999). Psychostimulant drugs like amphetamine, cocaine and phencyclidine preferentially stimulate dopamine transmission in the shell, but reduce the firing activity of dopamine neurons as a result of an interference with the dopamine reuptake carrier, accumulation of dopamine extracellularly and stimulation of dopamine autoreceptors.

Nicotine resembles non-psychostimulant drugs also for the dependence of its dopamine-stimulant property upon an endogenous tone on μ-opioid receptors (Tanda and Di Chiara, 1998) and on $5HT_3$-receptors (Carboni et al., 1989a).

Finally, repeated exposure to nicotine induces adaptive changes such as tolerance, and sensitization, in the level of dopamine in the shell and in the core of the nucleus accumbens that resemble those of other drugs of abuse.

8.1. Specificity of the stimulation of dopamine transmission in the nucleus accumbens shell by addictive drugs

The property of addictive drugs of stimulating dopamine transmission in the nucleus accumbens shell is specific in many respects. Thus, caffeine, a drug with psychostimulant and rewarding properties, but devoid of addictive properties dose-dependently increases dialysate dopamine in the prefrontal cortex, but is ineffective on dopamine transmission in the nucleus accumbens shell or core. The effect of caffeine on dopamine transmission in the prefrontal cortex might be secondary to its psychostimulant properties, which in turn might be the result of blockade of A_2 and A_1 adenosine receptors in limbic areas. Given the lack of addictive properties of caffeine (American Psychiatric Association, 1994), its failure to stimulate dopamine transmission in the nucleus accumbens shell is consistent with a role of nucleus accumbens shell dopamine in the dependence-liability of drugs.

Apart from psychostimulants, addictive drugs do not increase dopamine transmission in the prefrontal cortex. Thus, non-psychostimulant drugs including morphine, ethanol and nicotine, at doses which fully stimulate dopamine transmission in the nucleus accumbens shell, do not increase dopamine transmission in the medial prefrontal cortex where mesocortical dopamine neurons terminate (Bassareo et al., 1996). Cocaine and amphetamine, however, increase dialysate dopamine in the prefrontal cortex even more effectively than in the nucleus accumbens shell (Tanda et al., 1997b). The increase in extracellular dopamine in the prefrontal cortex induced by cocaine and amphetamine, however, is not due to an action on the dopamine carrier (as in the nucleus accumbens) but to blockade of the noradrenaline carrier, as shown in vivo by the concurrent increase of noradrenaline in the prefrontal cortex (Tanda et al., 1997b). GBR12909, a blocker of the dopamine carrier devoid of action on the noradrenaline carrier, while fully increasing dopamine in the nucleus accumbens, is ineffective in raising extracellular dopamine in the prefrontal cortex. Moreover, under selective blockade of the noradrenaline carrier by desipramine through reverse dialysis, cocaine fails to increase dopamine in the prefrontal cortex (Tanda et al., 1997b). These observations are explained by the 100 times difference in the ratio of noradrenaline terminals to dopamine terminals in the prefrontal cortex as compared to the NAc (Palkovits, 1979) and by the high efficiency (4 times more than NA itself) of the noradrenaline carrier as a transporter of dopamine (Raiteri et al., 1977). Therefore, in the prefrontal cortex, noradrenaline terminals provide a means for the clearance of dopamine from the extracellular space that is more efficient than that provided by dopamine terminals.

Although the role of the increase of dopamine in the prefrontal cortex for the addictive properties of cocaine and amphetamine is obscure, it is unlikely to be a major one given the lack of addictive liability or psychostimulant properties of antidepressants, that increase dopamine in the prefrontal cortex, but not in the nucleus accumbens (Tanda et al., 1994).

Finally, a number of aversive-anxiogenic drugs (e.g. picrotoxin, pentylenetetrazol, β-carbolines) stimulate in vivo dopamine transmission in the medial prefrontal cortex, but fail to affect dopamine transmission in the nucleus accumbens shell (Bassareo et al., 1996).

9. Dopamine release by motivational stimuli

Major differences do exist among different terminal areas of the dopamine system in the responsiveness of dopamine transmission to different motivational stimuli.

Primary appetitive stimuli (rewards) consistently increase dopamine transmission in the nucleus accumbens shell, in the prefrontal cortex and to a lesser extent in the nucleus accumbens core (Bassareo and Di Chiara, 1997, 1999; Tanda and Di Chiara, 1998). Primary aversive stimuli consistently stimulate dopamine transmission in the prefrontal cortex (Abercrombie et al., 1989), but either do not activate or even decrease dopamine transmission in the nucleus accumbens shell (Bassareo et al., 1996 and unpublished).

Secondary appetitive stimuli conditioned to the taste of a novel, palatable food phasically stimulate dopamine transmission in the medial prefrontal cortex and in the nucleus accumbens core, but not in the nucleus accumbens shell (Bassareo and Di Chiara, 1997, 1999); failure of conditional appetitive stimuli to activate dopamine transmission in the nucleus accumbens has been reported by various microdialysis studies (Hernandez and Hoebel, 1988; Radhakishun et al., 1988). Conditional aversive stimuli have been reported to reduce (Marks et al., 1991), increase or not affect (Young et al., 1993; Saulskaya and Marsden, 1995) dialysate dopamine in the nucleus accumbens. These studies, however, did not differentiate between nucleus accumbens shell and core.

From microdialysis observations, it appears that prefrontal cortex and nucleus accumbens core dopamine is stimulated by generic motivational stimuli either conditional or unconditional, positive or negative. In contrast, nucleus accumbens shell dopamine is activated by unconditional positive stimuli. Therefore, the properties of dopamine responsiveness in the nucleus accumbens shell are consistent with a relationship between phasic stimulation of dopamine transmission in this area and the action of rewards, but not of secondary, incentive stimuli.

9.1. Stimulation of dopamine transmission by aversive stimuli

An argument commonly raised against a specific relationship between dopamine and reward is that dopamine transmission in the nucleus accumbens is activated by aversive stimuli (Salamone, 1994; Gray et al., 1997). It is unlikely, however, that dopamine mediates the aversive properties of stimuli; eventually, it might be unrelated to the motivational valence of the stimulus being a generic expression of its arousing/activational properties; it is possible that dopamine activation is part of an adaptive response intended to counteract the learning and response impairing sequelae of aversive stimuli.

A more detailed analysis of this issue shows that aversive stimuli differ from rewards in their pattern of activation of dopamine transmission among different brain areas. While dopamine in the prefrontal cortex and in the nucleus accumbens core are monophasically increased by aversive as well as rewarding stimuli, the response of dopamine transmission in the nucleus accumbens shell is biphasic or retarded in the case of aversive stimuli and monophasic in the case of rewarding ones. Thus, dopamine decreases or does not change during the action of the aversive stimulus, increasing only after its termination. This is the case of forced swim, tail-pinch and aversive tastes (Di Chiara, 2000; Bassareo and Di Chiara, in preparation). It appears therefore that stimulation of dopamine in the nucleus accumbens shell is not directly related to the action of aversive stimuli, but to their termination, i.e. to safety and avoidance. Again, release of dopamine in the nucleus accumbens shell is uniquely linked to stimuli and states provided of primary survival value (rewards).

9.2. Adaptive properties of dopamine responsiveness to rewards

Stimulation of dopamine transmission habituates after a single exposure to a palatable food in the nucleus accumbens shell, but not in the prefrontal cortex or in the nucleus accumbens core (Bassareo and Di Chiara, 1997, 1999); this habituation has properties that differentiate it from acute tolerance, an adaptive change that has been shown to take place after repeated nicotine (see above). Thus, while acute tolerance fades between 2 and 3 h, habituation is still maximal after 24 h and slowly subsides so that it takes as long as 5 days for full recovery. Another adaptive change of dopamine release induced by palatable food is the inhibition exerted by a 40-min pre-exposure to appetitive stimuli predictive of food (food smell) on the stimulation of dopamine transmission in response to food consumption in the nucleus accumbens shell, but not in the prefrontal cortex nor in the nucleus accumbens core.

These adaptive changes should be compared with those obtained by extracellular recording of the firing of putative dopamine neurons in the ventral tegmentum of monkeys trained to acquire a delayed response task involving learning of the reward-predictive properties of a new discriminative stimulus (Schultz et al., 1993, 1997). In this task, dopamine neurons initially respond to a primary gustatory or to a secondary tactile stimulus but, as training progresses, this property is lost to be acquired by the new stimulus.

However, direct comparison between unit recording and microdialysis studies is made difficult by the lack of some essential information. Thus, while microdialysis studies have demonstrated the properties of dopamine transmission in specific terminal areas, this is not the case of single unit recording studies as those studies did not determine the site of termination of the recorded units (Schultz et al., 1997).

10. Role of dopamine in associative stimulus reward learning

The properties of dopamine responsiveness in the nucleus accumbens shell suggest a role in associative stimulus-reward learning (Di Chiara, 1999). Release of dopamine in the nucleus accumbens shell by unfamiliar and unpredicted primary appetitive stimuli (rewards) might serve to associate the discriminative properties of the rewarding stimulus with its biological outcome. This mechanism might be, in the case of dopamine in the nucleus accumbens shell, specifically related to feeding behaviour and responding to unfamiliar, palatable tastes. Thus, release of dopamine in the nucleus accumbens by an unfamiliar palatable food might serve to associate the taste of food to its post-ingestive, biological consequences. In this manner, depending on its outcome, the same taste can be accepted or rejected on a further encounter (Bassareo and Di Chiara, 1999).

Experimental studies involving lesions of dopamine neurons and manipulation of dopamine transmission by specific dopamine-receptor blockers are consistent with this hypothesis (Di Chiara, 1999). Early studies showed that D1 antagonists impair acquisition of conditioned place aversion (Acquas and Di Chiara, 1994; Acquas et al., 1989). Moreover, systemic as well as intra-shell (but not intra-core) infusion of the D1 antagonists SCH23390 and SCH39166 impairs conditioned taste aversion learning by preventing consolidation of the gustatory short-term memory trace to be associated with the aversive (lithium) state (Caulliez et al., 1996; Di Chiara et al., in preparation). Vice versa, systemic amphetamine facilitates taste aversion learning by facilitating consolidation (Di Chiara et al., in preparation). Various studies involving post-trial administration of dopamine receptor agonists and antagonists indicate that dopamine, plays a role in memory consolidation (Krivanek and McGaugh, 1969; Carr and White, 1984; Packard and White, 1991; Packard et al., 1994; White and

Viaud, 1991; Ploeger et al., 1994; Hitchcott et al, 1997a,b; Setlow and McGaugh, 1998).

We have hypothesized that the effect of neuroleptics on primary reinforcement, including the extinction-like effect which led Wise (1982) to the anhedonia hypothesis, is due to an action on the associative learning mechanism by which response-eliciting stimuli acquire and maintain their motivational value (stimulus-reward learning) (Di Chiara, 1999). Thus, in a straight alley paradigm, dopamine receptor blockade fails to reduce the response-eliciting properties (running the alley) of a CS + predicting reward availability (Horvitz and Ettenberg, 1991; McFarland and Ettenberg, 1995), but impairs reinforcement by the reward as shown by reduced responding on a second trial in the absence of dopamine-receptor blockade (McFarland and Ettenberg, 1995).

Under some circumstances, however, neuroleptics show a disrupting action on incentive responding and secondary reinforcement (see Blockburn et al., 1992, for review). This effect might be due to an action on sensory-motor functions typical of the response-competent portions of the striatum, i.e. the accumbens core and the caudate–putamen (Salamone, 1992).

11. Drugs of abuse as false neurochemical homologues of reward

Drug and non-drug rewards (e.g. food) share the property of activating dopamine transmission preferentially in the nucleus accumbens shell (Pontieri et al., 1995; Bassareo and Di Chiara, 1997, 1999; Tanda et al., 1997a). Non-psychostimulant drugs like nicotine, opiates, ethanol and cannabinoids also share with a conventional reinforcer like palatable food a μ-opioid component located in the ventral tegmentum (Tanda and Di Chiara, 1998). Therefore, drugs reproduce certain neurochemical effects of rewards that might be the substrate of their motivational effects (Di Chiara et al., 1993).

Addictive drugs, however, differ from rewards for the resistance of their stimulant effects in the nucleus accumbens shell dopamine transmission to adaptive modulation. Thus, in contrast to palatable food, drug-induced stimulation of dopamine transmission in the nucleus accumbens shell does not undergo long-lasting habituation (Hemby et al., 1997; Pettit and Justice, 1989, 1991; Wise et al., 1995a,b).

The substrate of these differences between drugs and rewards might be that drugs do not depend as rewards from stimulation of peripheral sensory receptors for the induction of their dopamine-stimulant effects; drugs enter the brain and directly activate the critical central mechanism that is only indirectly activated by rewards. As a result of this direct mechanism, drugs escape habituation that instead constrains the action of primary rewards.

Freedom from habituation would make addictive drugs capable of activating dopamine transmission in the nucleus accumbens shell in a manner that is not limited by previous drug history, but only by drug availability. Lack of such adaptive modulation is likely to constitute a major abnormality for a mechanism like phasic activation of dopamine transmission in the nucleus accumbens shell that is meant to subserve reward-related learning. We hypothesize that, as a result of the repetitive stimulation of dopamine transmission by self-administered drug, stimuli associated to drug-reward acquire excessive motivational value and become exceedingly effective to be utilized for instrumental responding, successfully competing with other stimuli in transfer from pavlovian to instrumental responding and in associative stimulus-response mechanisms.

Therefore, attribution of excessive motivational properties to drug-conditional stimuli as a result of non-habituating release of dopamine in the nucleus accumbens shell might provide the basis for the exclusive and dominant control that the drug comes to acquire over the subject's behaviour and that constitutes the most salient feature of addiction.

12. Differences between drugs of abuse and incentives

The acute effects of drugs of abuse on dopamine transmission, while similar to those of rewards, are quite different from those of incentive stimuli, stimuli that derive their motivational properties from learning of their association (conditioning) with a reward (Bolles, 1972; Bindra, 1974). Incentive stimuli do not stimulate dopamine transmission in the shell, but instead they do in the core and in the prefrontal cortex (Bassareo and Di Chiara, 1997, 1999).

Drugs of abuse and incentive stimuli also differ for the differential sensitivity of their behavioural effects to experimental impairment of dopamine transmission. Thus, while drug-induced locomotion and drug-enhanced conditioned reinforcement as well as psychostimulant self-administration are readily impaired by dopamine-receptor blockade and by lesions of dopamine neurons, this is not the case of spontaneous as well as conditioned locomotion (Beninger, 1983), conditioned reinforcement (Taylor and Robbins, 1986; Wolterink et al., 1993), conditioned approach in a place preference (Carr et al., 1989) or in a straight alley paradigm (Horvitz and Ettenberg, 1991; McFarland and Ettenberg, 1995). It appears that while responding to conditional stimuli is relatively resistant to impairment of dopamine transmission, unconditional drug-effects are particularly sensitive to it.

Those instances in which an impairment of responding for conditioned reinforcers has been obtained after dopamine receptor blockade (Phillips and Fibiger, 1979; Gray and Wise, 1980) can be explained as due to a non-specific performance impairment related to disruption of dopamine transmission in the dorsal striatum. Indeed,

this might be also the case of the 6-hydroxydopamine lesions of Corrigall et al. (1992).

The dopamine-independent nature of the response-eliciting properties of conditional incentive stimuli contradicts a commonly held view that attributes the incentive properties of these stimuli to their dopamine-stimulant properties (Robinson and Berridge, 1993) and further specifies the nature of the role of dopamine in the expression of motivation. In fact, the relative insensitivity of incentive responding to impairment of dopamine transmission speaks against a direct role of phasic dopamine transmission in the prefrontal cortex and in the core of the nucleus accumbens typically activated by incentive stimuli (Bassareo and Di Chiara, 1999) in actual response emission, favouring instead a role in the learning and maintenance of stimulus–response association for instrumental responding. Therefore, phasic dopamine transmission in the core of the nucleus accumbens and in the prefrontal cortex might be important for associative aspects of instrumental responding rather than for performance itself. Performance effects of dopamine receptor antagonists might be related instead to impairment of tonic dopamine transmission in the dorsal striatum.

13. Adaptive changes in dopamine responsiveness to nicotine and tobacco addiction

Adaptive changes in the responsiveness of dopamine transmission to drugs of abuse have been attributed to a role in the mechanism of drug-addiction. Thus, it has been assumed that drug-addiction is the result of non-associative, long-lasting, eventually irreversible changes (sensitization) in the responsiveness of the dopamine system to drug-conditioned incentive stimuli induced by the repeated exposure to the drug (Robinson and Berridge, 1993). Direct testing of this prediction, however, has provided negative results (Neisewander et al., 1996). Thus, operant presentation of a light cue predictive of cocaine intravenous infusion failed to release dopamine in the nucleus accumbens from the first extinction test (Neisewander et al., 1996). Moreover, a single non-contingent intravenous infusion of cocaine, which acts as a powerful incentive of lever pressing in cocaine-trained, but not in saline-yoked rats, increases dialysate dopamine in the nucleus accumbens to a lesser extent in the cocaine-trained than in the saline-yoked group (Neisewander et al., 1996). Recently, release of dopamine by amphetamine-conditioned stimuli has been observed by chronoamperometry with stearate electrodes but, due to the uncertainties over the nature of the signal recorded by this technique, these results require confirmation by a more reliable technique (Di Ciano et al., 1998b).

While the evidence that repeated exposure to drugs of abuse modifies the responsiveness of the dopamine system is essentially negative or uncertain, it is a matter of fact that repeated drug exposure induces changes in the responsiveness of dopamine transmission to the drug itself. This is also the case of nicotine. Therefore, if these changes play any role in drug-addiction, it is more likely that they do it by changing the dopamine response to the drug (Di Chiara, 1995) rather than, as postulated by Robinson and Berridge (1993), by changing the dopamine response to drug-conditioned stimuli.

It now appears that repeated drug exposure induces reciprocal changes of dopamine responsiveness to the drug in the two subdivisions of the nucleus accumbens (Cadoni and Di Chiara, 1999, 2000; Carboni et al., 2000a,b; Cadoni et al., 2000). In the case of nicotine, these differences are rather clear-cut and consist in enhancement of the stimulant effects of nicotine in the core with reduction of the effect in the shell (Cadoni and Di Chiara, 2000). We regard this change as potentially important for the evolution of dependence from an abnormal form of incentive responding into an abnormal form of habit responding (see below).

14. Nicotine dependence as dopamine-induced learning disorder

We regard addiction to tobacco as the final step of a dependence process resulting from abnormal drug-induced associative learning.

The initial step in this process is thought to be learning of the association between the rewarding properties of nicotine and otherwise neutral stimuli that acquire secondary positive motivational properties. These stimuli can be either intrinsic or extrinsic to nicotine itself and include those arising from substances associated to nicotine in smoke as well as from the context where nicotine's action takes place. Nicotine-associated stimuli thus become predictive of nicotine's availability and promote nicotine-seeking behaviour and tobacco smoking. This process of associative stimulus-reward learning is facilitated by nicotine itself through its ability to stimulate dopamine release in the nucleus accumbens shell.

Nicotine-induced release of dopamine in the nucleus accumbens undergoes acute tolerance, but this change is fully reversible in 3 h (Maisonneuve et al., 1997). In contrast, nucleus accumbens dopamine release by a non-drug reward like palatable food is strongly depressed already 2 h and up to 24 h after the first exposure (Bassareo and Di Chiara, 1997). This differential liability to habituation of the dopamine stimulant effect of rewards as compared to drugs of abuse might be critical for the addictive properties of drugs. In fact, by releasing dopamine non-decrementally in the nucleus accumbens shell upon repeated exposure, addictive drugs including nicotine might abnormally facilitate stimulus-reward learning, thus promoting the acquisition of excessive motivational properties by stimuli associated to drug exposure. As a result of this

mechanism, nicotine would acquire upon repeated administration that excessive control over behaviour that is a landmark of addiction (Di Chiara, 1998, 1999).

Stimuli that have acquired conditional incentive properties by stimulus-reward learning become, by a process of transfer from pavlovian to instrumental learning, conditioned reinforcers for instrumental responding (Dickinson, 1994). Stimulation of dopamine transmission facilitates the transfer from pavlovian to instrumental responding and the overall expression of instrumental responding (Robbins, 1975; Cador et al., 1989). Thus, dopamine, in addition to facilitate stimulus-reward learning, might play a role in stimulus–response association (Bassareo and Di Chiara, 1999). We suggest that these two associative learning mechanisms are related to dopamine transmission in different subdivisions of the nucleus accumbens, the first in the shell, the second in the core. Although such an action has not been specifically demonstrated for nicotine, we postulate that nicotine, by releasing dopamine in the nucleus accumbens core, also facilitates transfer from pavlovian to instrumental responding and learning of stimulus–response associations.

In the initial phase of training for instrumental responding, response is reinforced by its outcome (incentive responding). After extensive training, however, responding becomes relatively independent from outcome being run on the basis of action schemata triggered by stimuli preceding responding (Dickinson, 1994). This form of instrumental responding, called habit responding, is utilized in the most diverse activities of every day life such as driving a car, writing, typing, playing piano, etc. and might be the form of instrumental behaviour that takes place in drug self-administration including nicotine self-administration in animals and humans (Altman et al., 1996; Di Chiara, 1998). In animals, a typical sign of habit responding consists in resistance to outcome devaluation (Dickinson and Balleine, 1995); this is indeed what is observed in rats when nicotine is replaced with saline under intermittent schedules of intravenous self-administration (see Di Chiara, 2000 for discussion).

In humans, tobacco smoking has been viewed as an abnormal form of habit responding given the fact that smoking is poorly controlled by consequences such as amount of nicotine inhaled and is instead automatically run following triggering by conditional smoking-related cues (Tiffany, 1990).

The circumstance that tobacco smoking is a form of habit responding and that, as such, is independent from its outcome does not mean that nicotine plays a minor role in tobacco addiction; removal of nicotine from tobacco while not affecting smoking behaviour in the short run, leads to extinction of smoking in the long run. The reason for this might be that conditional stimuli that trigger the habitual response depend from associative stimulus-reward learning for maintaining their conditional motivational properties. This suggests that release of dopamine in the shell, which is thought to be the substrate of this process, maintains its critical importance in advanced stages of addiction. It appears therefore that in chronic smoking, the outcome of instrumental behaviour, i.e. the rewarding actions of nicotine, are simply moved away from responding, but still retain their role as the final goal of behaviour.

The biological substrate for these behavioural changes might be provided by the changes in the responsiveness of dopamine transmission to nicotine that take place during the course of exposure to tobacco smoke.

Initial acute exposure to nicotine stimulates dopamine preferentially in the nucleus accumbens shell (Pontieri et al., 1996). Intermittent discontinuous exposure to nicotine as in the case of peak smokers (Russell, 1990) results in rapidly reversible desensitization resulting in acute tolerance (Maisonneuve et al., 1994) to nicotine-induced stimulation of dopamine release in the nucleus accumbens shell. Instead, repeated continuous exposure to nicotine during the day, as in through smokers, results in a complex exposure to nicotine characterized by peaks, which correspond to cigarette smoking, on a baseline of nicotine that builds up in a stepwise fashion at each cigarette smoking during the day to decrease during the night, when smoking ceases. The presence of a steady-state level of nicotine, while eventually insufficient to phasically stimulate dopamine release in the nucleus accumbens is sufficient to induce desensitization. However, as a result of a relative resistance to inactivation of nicotinic acetylcholine receptors containing certain subunits (α_3/α_6 ?) (Olale et al., 1997), desensitization of dopamine transmission is not complete even in a chronic smoker; this allows dopamine release in response to nicotine to take place also after chronic exposure (Carboni et al., 2000a). Under these conditions, the extent of phasic dopamine release directly associated to cigarette smoking should be an inverse function of the steady-state level of nicotine. Since the steady-state level of nicotine in a chronic smoker progressively increases during the day, the phasic response of dopamine transmission in the nucleus accumbens to smoking should be minimal at night and maximal in response to the first morning cigarette (Dani and Heinemann, 1996).

Another adaptive change to repeated nicotine exposure consists in sensitization.

Schedules of nicotine exposure that induce sensitization differentially affect dopamine responsiveness in the shell and in the core of the nucleus accumbens (Cadoni and Di Chiara, 2000). Thus, behavioural sensitization to nicotine is associated to an increased responsiveness in the nucleus accumbens core and in a reduction in the shell.

We speculate that the reversal of the shell/core ratio of dopamine release stimulation in the nucleus accumbens by nicotine might be the basis for learning of an abnormal form of habit responding. This change would mark a switch of responding from the explicit, conscious modality of incentive responding into the compulsive, automatic mode of abnormal habit responding, typical of addiction

(Tiffany, 1990). This responding modality, however, should not be viewed as the sole behavioural repertoire of the addicted smoker. Depending on the availability of tobacco, responding can switch between automatic habit responding, driven by action schemata, and incentive responding related to subjective effects of smoke and associated to conscious expectancies termed in common parlace as well as in more specialized contexts, craving (Tiffany, 1990).

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References

Abercrombie, E.A., Keefe, K.A., Di Frischia, D.A., Zigmond, M.J., 1989. Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens and medial frontal cortex. J. Neurochem. 52, 1655–1658.

Acquas, E., Carboni, E., Leone, P., Di Chiara, G., 1989. SCH23390 blocks drug-conditioned place-preference and place-aversion: anhedonia (lack of reward) or apathy (lack of motivation) after dopamine receptor blockade? Psychopharmacology 99, 151–155.

Acquas, E., Di Chiara, G., 1994. D_1 receptors blockade stereospecifically impairs the acquisition of drug-conditioned place-preference and place-aversion. Behav. Pharmacol. 5, 555–569.

Alkondon, M., Reinhardt, S., Lobron, C., Hermsen, B., Maelicke, A., Albuquerque, E.X., 1994. Diversity of nicotinic acetylcholine receptors in rat hippocampal neurons: II. The rundown and inward rectification of agonist-elicited whole-cell currents and identification of receptor subunits by in situ hybridization. J. Pharmacol. Exp. Ther. 271, 494–506.

Altman, J., Everitt, B.J., Glautier, S., Markou, A., Nutt, D., Oretti, R., Phillips, G.D., Robbins, T.W., 1996. The biological, social, and clinical bases of drug addiction: commentary and debate. Psychopharmacology 125, 285–345.

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders. 3rd edn. American Psychiatric Association, Washington, DC, revised.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th edn. American Psychiatric Association, Washington, DC.

Ando, K., Yanagita, T., 1978. The discriminative stimulus properties of intravenously administered cocaine in rhesus monkeys. In: Colpaert, F.C., Rosecrans, J.A. (Eds.), Stimulus Properties of Drugs: Ten Years of Progress. Elsevier, Amsterdam, pp. 125–136.

Arroyo-Jimenez, M.M., Bourgeois, J.-P., Marubio, L.M., LeSourd, A.M., Ottersenn, O.P., Rinvik, P., Faire, A., Changeux, J.-P., 1999. Ultrastructural localization of the a4-subunit of the neuronal acetylcholine nicotinic receptor in the rat substantia nigra. J. Neurosci. 19, 6475–6487.

Azam, L., Castaneda, D., Chen, Y., Leslie, F.M., 1999. Expression of neuronal nicotinic acetylcholine receptor subunit mRNAS within rat midbrain. Soc. Neurosci. 25, 187.

Bardo, M.T., Bevins, R.A., Klebaur, J.E., Crooks, P.A., Dwoskin, L.P., 1997. (−)-Nornicotine partially substitutes for (+)-amphetamine in a drug discrimination paradigm in rats. Pharmacol. Biochem. Behav. 58, 1083–1087.

Bassareo, V., Di Chiara, G., 1997. Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum. J. Neurosci. 17, 851–861.

Bassareo, V., Di Chiara, G., 1999. Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. Neuroscience 89, 637–641.

Bassareo, V., Tanda, G., Petromilli, P., Giua, C., Di Chiara, G., 1996. Non-psychostimulant drugs of abuse and anxiogenic drugs activate with differential selectivity dopamine transmission in the nucleus accumbens and in the medial prefrontal cortex. Psychopharmacology 124, 293–299.

Bauco, P., Wise, R.A., 1994. Potentiation of lateral hypothalamic and midline mesencephalic brain stimulation reinforcement by nicotine: examination of repeated treatment. J. Pharmacol. Exp. Ther. 271, 294–301.

Beninger, R.J., 1983. The role of dopamine in locomotor activity and learning. Brain Res. 6, 173–196.

Benwell, M.E., Balfour, D.J., Birrell, C.E., 1995. Desensitization of the nicotine-induced mesolimbic dopamine responses during constant infusion with nicotine. Br. J. Pharmacol. 144, 454–460.

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.

Bindra, D., 1974. A motivational view of learning, performance, and behavior modification. Psychol. Rev. 81, 199–213.

Blackburn, J.R., Pfaus, J.G., Phillips, A.G., 1992. Dopamine functions in appetitive and defensive behaviours. Progress in Neurobiology 39, 247–279.

Bolles, R.C., 1972. Reinforcement, expectancy, and learning. Psychol. Rev. 79, 394–409.

Brioni, J.D., Kim, D.J., O'Neill, A.B., Williams, J.E., Decker, M.W., 1994. Clozapine attenuates the discriminative stimulus properties of (−)-nicotine. Brain Res. 643, 1–9.

Cadoni, C., Di Chiara, G., 1999. Reciprocal changes in dopamine responsiveness in the nucleus accumbens shell and core and in the dorsal caudate–putamen in rats sensitized to morphine. Neuroscience 90, 447–455.

Cadoni, C., Di Chiara, G., 2000. Differential changes in accumbens shell and core dopamine in behavioural sensitization to nicotine. Eur. J. Pharmacol., (in press).

Cadoni, C., Solinos, M., Di Chiara, G., 2000. Psychostimulant sensitization differential changes in accumbal shell and core dopamine. Eur. J. Pharmacol. 388, 69–76.

Cador, M., Robbins, T.W., Everitt, B.J., 1989. Involvement of amygdala in stimulus–reward association: interaction with the ventral striatum. Neuroscience 30, 77–86.

Caine, S.B., Koob, G.F., 1994. Effects of mesolimbic dopamine depletion on responding maintained by cocaine and food. J. Exp. Anal. Behav. 61, 213–221.

Calcagnetti, D.J., Schechter, M.D., 1994. Nicotine place preference using the biased method of conditioning. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 18, 925–933.

Carboni, E., Acquas, E., Frau, R., Di Chiara, G., 1989a. Differential inhibitory effects of a $5HT_3$ antagonist on drug-induced stimulation of dopamine release. Eur. J. Pharmacol. 164, 515–519.

Carboni, E., Acquas, E., Leone, P., Di Chiara, G., 1989b. $5HT_3$ receptor antagonists block morphine- and nicotine- but not amphetamine-induced reward. Psychopharmacology 97, 175–178.

Carboni, E., Bortone, L., Giua, C., Di Chiara, G., 2000a. Dissociation of physical abstinence signs from changes in extraacellular dopamine in the nucleus accumbens and in the prefrontal cortex of nicotine dependent rats. Drug Alcohol Depend. 58, 93–102.

Carboni, E., Silvagni, A., Rolando, M.T.P., Di Chiara, G., 2000b. Stimulation of in vivo dopamine transmission in the bed nucleus of stria terminalis by addictive drugs. J. Neurosci., (in press).

Carr, G.D., Fibiger, H.C., Phillips, A.G., 1989. Conditioned place preference as a measure of drug reward. In: Liebman, J.M., Cooper, S.J. (Eds.), The Neuropharmacological Basis of Reward. Oxford Univ. Press, New York, pp. 264–319.

Carr, G.D., White, N.M., 1984. The relationship between stereotypy and memory improvement produced by amphetamine. Psychopharmacology 82, 203–209.

Carroll, M.E., Lac, S.T., Asencio, M., Keenan, R.M., 1989. Nicotine dependence in rats. Life Sci. 45, 1381–1388.

Caulliez, R., Meile, M.-J., Nicolaidis, S., 1996. A lateral hypothalamic D1 dopaminergic mechanism in conditioned taste aversion. Brain Res. 729, 234–245.

Chance, W.T., Murfin, D., Krynock, G.M., Rosecrans, J.A., 1977. A description of the nicotine stimulus and tests of its generalization to amphetamine. Psychopharmacology 55, 19–26.

Chandler, C.J., Stolerman, I.P., 1997. Discriminative stimulus properties of the nicotinic agonist cytisine. Psychopharmacology 129, 257–264.

Clarke, P.B.S., Fibiger, H.C., 1987. Apparent absence of nicotine-induced conditioned place preference in rats. Psychopharmacology 92, 84–88.

Clarke, P.B.S., Fu, D.S., Jakubovic, A., Fibiger, H.C., 1988a. Evidence that mesolimbic dopaminergic activation underlies the locomotor stimulant action of nicotine in rats. J. Pharmacol. Exp. Ther. 246, 701–708.

Clarke, P.B.S., Jakubovic, A., Fibiger, H.C., 1988b. Anatomical analysis of the involvement of mesolimbic dopamine in the locomotor stimulant actions of D-amphetamine and apomorphine. Psychopharmacology 96, 511–520.

Corrigall, W.A., 1999. Nicotine self-administration in animal as a dependence model. Nicotine Tob. Res. 1, 11–20.

Corrigall, W.A., Coen, K.M., 1989. Nicotine maintains self-administration in rats on a limited-access schedule. Psychopharmacology 99, 473–478.

Corrigall, W.A., Coen, K.M., 1991a. Opiate antagonists reduce cocaine but not nicotine self-administration. Psychopharmacology 104, 167–170.

Corrigall, W.A., Coen, K.M., 1991b. Selective dopamine antagonists reduce nicotine self-administration. Psychopharmacology 104, 171–176.

Corrigall, W.A., Coen, K.M., 1994a. Dopamine mechanisms play at best a small role in the nicotine discriminative stimulus. Pharmacol. Biochem. Behav. 48, 817–820.

Corrigall, W.A., Coen, K.M., 1994b. Nicotine self-administration and locomotor activity are not modified by the 5-HT_3 antagonists ICS 205-930 and MDL 72222. Pharmacol. Biochem. Behav. 49, 67–71.

Corrigall, W.A., Coen, K.M., Adamson, K.L., 1994. Self-administered nicotine activates the mesolimbic dopamine system through the ventral segmental area. Brain Res. 653, 278–284.

Corrigall, W.A., Franklin, K.B., Coen, K.M., Clarke, P.B., 1992. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology 107, 285–289.

Damsma, G., Day, J., Fibiger, H.C., 1989. Lack of tolerance to nicotine-induced dopamine release in the nucleus accumbens. Eur. J. Pharmacol. 168, 363–368.

Dani, J.A., Heinemann, S., 1996. Molecular and cellular aspects of nicotine abuse. Neuron 16, 905–908.

Dawe, S., Gerada, C., Russell, M.A., Gray, J.A., 1995. Nicotine intake in smokers increases following a single dose of haloperidol. Psychopharmacology 117, 110–115.

De la Garza, R., Johanson, C.E., 1983. The discriminative stimulus properties of cocaine in the rhesus monkey. Pharmacol. Biochem. Behav. 19, 145–148.

De la Garza, R., Johanson, C.E., 1985. Discriminative stimulus properties of cocaine in pigeons. Psychopharmacology 85, 23–30.

Deneris, E.S., Boulter, J., Swanson, L.W., Patrick, J., Heinemann, S., 1989. B_3: a new member of nicotinic acetylcholine receptor gene family is expressed in brain. J. Biol. Chem. 264, 6268–6272.

Dewey, S.L., Brodie, J.D., Gerasimov, B.M., Horan, B., Gardner, E.L., Ashby, C.R., 1999. A pharmacologic strategy for the treatment of nicotine addiction. Synapse 31, 76–86.

Di Chiara, G., 1990. In vivo brain dialysis of neurotransmitters. Trends Pharmacol. Sci. 11, 116–121.

Di Chiara, G., 1995. The role of dopamine in drug abuse viewed from the perspective of its role in motivation. Drug Alcohol Depend. 38, 95–137.

Di Chiara, G., 1998. A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. J. Psychopharmacol. 12, 54–67.

Di Chiara, G., 1999. Drug addiction as dopamine-dependent associative learning disorder. Eur. J. Pharmacol. 375, 13–30.

Di Chiara, G., 2000. Behavioural pharmacology and neurobiology of nicotine reward and dependence. In: Clementi, F., Fornasari, D., Gotti, C. (Eds.), Handbook Exp. Pharmacology Vol. 144 Springer, Heidelberg.

Di Chiara, G., Acquas, E., Tanda, G., Cadoni, C., 1993. Drugs of abuse: biochemical surrogates of specific aspects of natural reward?. Biochem. Soc. Symp. 59, 65–81.

Di Chiara, G., Acquas, E., Tanda, G., 1996a. Ethanol a neurochemical surrogate of conventional reinforcers the dopamine–opioid link. Alcohol 13, 13–17.

Di Chiara, G., Imperato, A., 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. U. S. A. 85, 5274–5278.

Di Chiara, G., Loddo, P., Tanda, G., 1999. Reciprocal changes in prefrontal and limbic dopamine responsiveness to aversive and rewarding stimuli after chronic mild stress: implications for the psychobiology of depression. Biol. Psychiatry 46, 1624–1633.

Di Chiara, G., Tanda, G., Carboni, E., 1996b. Estimation of in vivo neurotransmitter release by brain microdialysis: the issue of validity. Behav. Pharmacol. 7, 640–657.

Di Ciano, P., Blaha, C.D., Phillips, A.G., 1998. Conditioned changes in dopamine oxidation currents in the nucleus accumbens of rats by stimuli paired with self-administration or yoked-administration of D-amphetamine. Eur. J. Neurosci. 10, 1121–1127.

Dickinson, A., 1994. Instrumental conditioning. In: Mackintosh, N. (Ed.), Animal Learning and Cognition. Academic Press, San Diego, pp. 45–79.

Dickinson, A., Balleine, B., 1995. Motivational control of instrumental action. Curr. Dir. Psychol. Sci. 4, 162–167.

Dineley-Miller, K., Patrick, J., 1992. Gene transcripts for the nicotinic acetylcholine receptor subunit β4 are distributed in multiple areas of the rat central nervous system. Mol. Brain Res. 16, 339–344.

Falk, J.L., 1971. The nature and determinants of adjunctive behavior. Physiol. Behav. 6, 577–588.

Fu, Y., Matta, S.G., Sharp, B.M., 1999a. Local alpha-bungarotoxin (α-BTX)-sensitive nicotinic receptors modulate nicotine-induced dopamine (DA) release in the nucleus accumbens (NACC). Soc. Neurosci. 25, 187.

Fu, Y., Matta, S.G., Sharp, B.M., 1999b. Local α-bungarotoxin-sensitive nicotinic receptors modulate hippocampal norepinephrine release by systemic nicotine. JPET 289, 133–139.

Fudala, P.J., Iwamoto, E.T., 1986. Further studies on nicotine-induced conditioned place preference in the rat. Pharmacol. Biochem. Behav. 25, 1041–1049.

Fudala, P.J., Teoh, K.W., Iwamoto, E.T., 1985. Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol. Biochem. Behav. 22, 237–241.

Gasior, M., Shoaib, M., Yasar, S., Jaszyna, M., Goldberg, S.R., 1999. Acquisition of nicotine discrimination and discriminative stimulus effects of nicotine in rats chronically exposed to caffeine. J. Pharmacol. Exp. Ther. 288, 1053–1073.

Gilbert, R.M., 1978. Schedule-induced self-administration of drugs. In: Blackman, D.E., Sanger, D.J. (Eds.), Contemporary Research in Behavioral Pharmacology. Plenum, New York.

Goldner, F., Dineley, K., Patrick, J., 1997. Immunohistochemical localization of the nicotinic acetylcholine receptor subunit α6 dopaminergic neurons in the substantia nigra and ventral tegmental area. NeuroReport 8, 2739–2742.

Gray, T., Wise, R.A., 1980. Effects of pimozide on lever-pressing behavior maintained on an intermittent reinforcement schedule. Pharmacol. Biochem. Behav. 12, 931–935.

Gray, J.A., Young, A.M., Joseph, M.H., 1997. Dopamine's role. Science 278, 1548–1549, [letter].

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.

Hemby, S.E., Co, C., Koves, T.R., Smith, J.E., Dworkin, S.I., 1997. Differences in extracellular dopamine concentrations in the nucleus accumbens during response-dependent and response-independent cocaine administration in the rat. Psychopharmacology 133, 7–16.

Henningfield, J.E., Goldberg, S.R., 1983a. Control of behavior by intravenous nicotine injections in human subjects. Pharmacol. Biochem. Behav. 19, 1021–1026.

Henningfield, J.E., Goldberg, S.R., 1983b. Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol. Biochem. Behav. 19 (6), 989–992.

Hernandez, L., Hoebel, B.G., 1988. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci. 42, 1705–1712.

Hildebrand, B.E., Nomikos, G.G., Hertel, P., Schilstrom, B., Svensson, T.H., 1997. Reduced dopamine output in the nucleus accumbens but not in the medial prefrontal cortex in rats displaying a mecamylamine-precipitated nicotine withdrawal syndrome. Brain Res. 779, 214–225.

Hill, J.A. Jr., Zoli, M., Bourgeois, J.P., Changeux, J.P., 1993. Immunocytochemical localization of a neuronal nicotinic receptor: the β2 subunit. J. Neurosci. 13, 1551–1568.

Hitchcott, P.K., Bonardi, C.M.T., Phillips, G.D., 1997a. Enhanced stimulus-reward learning by intra-amygdala administration of a D3 dopamine receptor agonist. Psychopharmacology 133, 240–248.

Hitchcott, P.K., Harmer, C.J., Phillips, G.D., 1997b. Enhanced acquisition of discriminative approach following intra-amygdala D-amphetamine. Psychopharmacology 132, 237–246.

Horan, B., Smith, M., Gardner, E.L., Lepore, M., Ashby, C.R. Jr., 1997. (−)-Nicotine produces conditioned place preference in Lewis, but not Fischer 344 rats. Synapse 26, 93–94.

Horvitz, J.C., Ettenberg, A., 1991. Conditioned incentive properties of a food-paired conditioned stimulus remain intact during dopamine receptor blockade. Behav. Neurosci. 105, 536–541.

Huston-Lyons, D., Kornetsky, C., 1992. Effects of nicotine on the threshold for rewarding brain stimulation in rats. Pharmacol. Biochem. Behav. 41, 755–759.

Huston-Lyons, D., Sarkar, M., Kornetsky, C., 1993. Nicotine and brain-stimulation reward: interactions with morphine, amphetamine and pimozide. Pharmacol. Biochem. Behav. 46, 453–457.

Imperato, A., Mulas, A., Di Chiara, G., 1986. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur. J. Pharmacol. 132, 337–338.

Ivanova, S., Greenshaw, A.J., 1997. Nicotine-induced decreases in VTA electrical self-stimulation thresholds: blockade by haloperidol and mecamylamine but not scopolamine or ondansetron. Psychopharmacology 134, 187–192.

Izenwasser, S., Jacocks, H.M., Rosenberger, J.G., Cox, B.M., 1991. Nicotine indirectly inhibits [^{3}H]dopamine uptake at concentrations that do not directly promote [^{3}H]dopamine release in rat striatum. J. Neurochem. 56, 603–610.

Krivanek, J.A., McGaugh, J.L., 1969. Facilitating effects of pre- and posttrial amphetamine administration on discrimination learning in mice. Agents Actions 1, 36–42.

Ksir, C., Mellor, G., Hart, C., Gerhardt, G.A., 1995. Nicotine enhances dopamine clearance in C rat nucleus accumbens. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 19, 151–156.

Jorenby, D.E., Steinpreis, R.E., Sherman, J.E., Baker, T.B., 1990. Aversion instead of preference learning indicated by nicotine place conditioning in rats. Psychopharmacology 101, 533–538.

Joseph, M.H., Peters, S.L., Gray, J.A., 1993. Nicotine blocks latent inhibition in rats: evidence for a critical role of increased functional activity of dopamine in the mesolimbic system at conditioning rather than pre-exposure. Psychopharmacology 110, 187–192.

Killcross, A.S., Dickinson, A., Robbins, T.W., 1994a. Amphetamine-induced disruptions of latent inhibition are reinforcer mediated: implications for animal models of schizoohrenic attentional dysfunction. Psychopharmacology 115, 185–195.

Killcross, A.S., Dickinson, A., Robbins, T.W., 1994b. Effects of the neuroleptic α-flupenthixol on latent inhibition in aversively and appetitively motivated paradigms: evidence for dopamine–reinforcer interactions. Psychopharmacology 115, 196–205.

Leikola-Pelho, T., Jackson, D.M., 1992. Preferential stimulation of locomotor activity by ventral tegmental microinjections of (−)nicotine. Pharmacol. Toxicol. 70, 50–52.

LeNovere, N., Zoli, M., Changeux, J.P., 1996. Neuronal nicotinic receptors alpha 6 subunit mRNA is selectively concentrated in catecholaminergic nuclei of the rat brain. Eur. J. Neurosci. 8, 2428–2439.

Louis, M., Clarke, P.B., 1998. Effect of ventral tegmental 6-hydroxydopamine lesions on the locomotor stimulant action of nicotine in rats. Neuropharmacology 37, 1503–1513.

Maisonneuve, I.M., Mann, G.L., Deibel, C.R., 1997. Ibogaine and the dopaminergic response to nicotine. Psychopharmacology 129, 249–256.

Mansbach, R.S., Rovetti, C.C., Freedland, C.S., 1998. The role of monoamine neurotransmitter systems in the nicotine discriminative stimulus. Drug Alcohol Depend. 52, 125–134.

Marks, M.J., Campbell, S.M., Romm, E., Collins, A.C., 1991. Genotype influences the development of tolerance to nicotine in the mouse. J. Pharmacol. Exp. Ther. 259, 392–402.

McEvoy, J.P., Freudenreich, O., Levin, E.D., Rose, J.E., 1995. Haloperidol increases smoking in patients with schizophrenia. Psychopharmacology 119, 124–126.

McFarland, K., Ettenberg, A., 1995. Haloperidol differentially affects reinforcement and motivational processess in rats running an alley for intravenous heroin. Psychopharmacology 122, 346–350.

Mereu, G., Yoon, K.-W.P., Boi, V., Gessa, G.L., Naes, L., Westfall, T.C., 1987. Preferential stimulation of ventral tegmental area dopaminergic neurons by nicotine. Eur. J. Pharmacol. 141, 395–399.

Museo, E., Wise, R.A., 1990a. Microinjection of a nicotinic agonist into dopamine terminal fields: effects on locomotion. Pharmacol. Biochem. Behav. 37, 113–116.

Museo, E., Wise, R.A., 1990b. Locomotion induced by ventral tegmental microinjections of a nicotinic agonist. Pharmacol. Biochem. Behav. 37, 735–737.

Museo, E., Wise, R.A., 1995. Cytisine-induced behavioral activation: delineation of neuroanatomical locus of action. Brain Res. 670, 257–263.

Neisewander, J.L., O'Dell, L.E., Ly, M.A., Tran-Nguyen, T.L., Edward Castañeda, M.A., Fuchs, R.A., 1996. Dopamine overflow in the nucleus accumbens during extinction and reinstatement of cocaine. Neuropsychopharmacology 15, 506–514.

Nisell, M., Marcus, M., Nomikos, G.G., Svensson, T.H., 1997a. Differential effects of acute and chronic nicotine on dopamine output in the core and shell of the rat nucleus accumbens. J. Neural. Transm. 104, 1–10.

Nisell, M., Nomikos, G.G., Chergui, K., Grillner, P., Svensson, T.H., 1997b. Chronic nicotine enhances basal and nicotine-induced Fos

immunoreactivity preferentially in the medial prefrontal cortex of the rat. Neuropsychopharmacology 17, 151–161.
Nisell, M., Nomikos, G.G., Hertel, P., Panagis, G., Svensson, T.H., 1996. Condition-independent sensitization of locomotor stimulation and mesocortical dopamine release following chronic nicotine treatment in the rat. Synapse 22, 369–381.
Nisell, M., Nomikos, G.G., Svensson, T.H., 1994a. Infusion of nicotine in the ventral tegmental area or the nucleus accumbens of the rat differentially affects accumbal dopamine release. Pharmacol. Toxicol. 75, 348–352.
Nisell, M., Nomikos, G.G., Svensson, T.H., 1994b. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. Synapse 16, 36–44.
O'Brien, C.P., 1996. Drug addiction and drug abuse. In: Goodman, L.S., Gilman, A. (Eds.), The Pharmacological Basis of Therapeutics. Mc Graw Hill, New York.
Olale, F., Gerzanich, V., Kuryatov, A., Wang, F., Lindstrom, J., 1997. Chronic nicotine exposure differentially affects the function of human $\alpha 3$, $\alpha 4$, and $\alpha 7$ neuronal nicotinic receptor subtypes. J. Pharmacol. Exp. Ther. 283, 675–683.
O'Neill, M.F., Dourish, C.T., Iversen, S.D., 1991. Evidence for an involvement of D_1 and D_2 dopamine receptors in mediating nicotine-induced hyperactivity in rats. Psychopharmacology 104, 343–350.
Packard, M.G., Cahill, L., McGaugh, J.L., 1994. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. PNAS 91, 8477–8481.
Packard, M.G., White, N.M., 1991. Dissociation of hippocampal and caudate nucleus memory systems by post-training intracerebral injection of dopamine agonists. Behav. Neurosci. 105, 295–306.
Palkovits, M., 1979. In: Dopamine Levels of Individual Brain Regions: Biochemical Aspects of DA Distribution in the Central Nervous System. Academic Press, London, pp. 343–356.
Panagis, G., Nisell, M., Nomikos, G.G., Chergui, K., Svensson, T.H., 1996. Nicotine injections into the ventral tegmental area increase locomotion and Fos-like immunostaining in the nucleus accumbens of the rat. Brain Res. 730, 133–142.
Parker, L.A., 1992. Place conditioning in a three- or four-choice apparatus: role of stimulus novelty in drug-induced place conditioning. Behav. Neurosci. 106, 294–306.
Perkins, K.A., DiMarco, A., Grobe, J.E., Scierka, A., Stiller, R.L., 1994a. Nicotine discrimination in male and female smokers. Psychopharmacology 116 (4), 407–413.
Perkins, K.A., Epstein, L.H., Grobe, J., Fonte, C., 1994b. Tobacco abstinence, smoking cues, and the reinforcing value of smoking. Pharmacol. Biochem. Behav. 47, 107–112.
Perkins, K.A., Grobe, J.E., Fonte, C., Goettler, J., Caggiula, A.R., Reynolds, W.A., Stiller, R.L., Scierka, A., Jacob, R.G., 1994c. Chronic and acute tolerance to subjective, behavioral and cardiovascular effects of nicotine in humans. J. Pharmacol. Exp. Ther. 270 (2), 628–638.
Perkins, K.A., Sexton, J.E., Reynolds, W.A., Grobe, J.E., Fonte, C., Stiller, R.L., 1994d. Comparison of acute subjective and heart rate effects of nicotine intake via tobacco smoking vs. nasal spray. Pharmacol. Biochem. Behav. 47, 295–299.
Perkins, K.A., Sexton, J.E., Stiller, R.L., Fonte, C., Di Marco, A., Goettler, J., Scierka, A., 1994e. Subjective and cardiovascular responses to nicotine combined with caffeine during rest and casual activity. Psychopharmacology 113, 438–444.
Petitt, H.O., Ettenberg, A., Bloom, F.E., Koob, G.F., 1984. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology 84, 167–173.
Petitt, H.O., Justice, J.B., 1991. Effect of dose on cocaine self-administration behavior and dopamine levels in the nucleus accumbens. Brain Res. 539, 94–102.
Petitt, H.O., Justice, J.B. Jr., 1989. Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. Pharmacol. Biochem. Behav. 34, 899–904.
Phillips, A.G., Fibiger, H.C., 1979. Decreased resistance to extinction after haloperidol: implications for the role of dopamine in reinforcement. Pharmacol. Biochem. Behav. 10, 751–761.
Picciotto, M.R., Zoli, M., Rimondini, R., Lena, C., Marubio, L.M., Pich, E.M., Fuxe, K., Changeux, J.P., 1998. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 391, 173–177.
Pidoplichko, V.I., DeBiasi, M., Williams, J.T., Dani, J.A., 1997. Nicotine activates and desensitizes midbrain dopamine neurons. Nature 390, 401–404.
Ploeger, G.E., Spruijt, B.M., Cools, A.R., 1994. Spatial localization in the Morris watermaze task in rats: acquisition is affected by intra-accumbens injections of the dopaminergic antagonist haloperidol. Behav. Neurosci. 108, 927–934.
Pontieri, F.E., Tanda, G., Di Chiara, G., 1995. Intravenous cocaine, morphine and amphetamine preferentially increase extracellular dopamine in the ''shell'' as compared with the ''core'' of the rat nucleus accumbens. Proc. Natl. Acad. Sci. U. S. A. 92, 12304–12308.
Pontieri, F.E., Tanda, G., Orzi, F., Di Chiara, G., 1996. Effects of nicotine on the nucleus accumbens and similarities to those of addictive drugs. Nature 382, 255–257.
Preston, K.L., Bigelow, G.E., 1991. Subjective and discriminative effects of drugs. Behav. Pharmacol. 2, 293–313.
Radhakishun, F.S., van Ree, J.M., Westerink, B.H.C., 1988. Scheduled eating increases dopamine release in the nucleus accumbens of food deprived rats as assessed with on-line brain dialysis. Neurosci. Lett. 85, 351–356.
Raiteri, M., Del Carmine, R., Bertollini, A., Levi, G., 1977. Effects of sympathomimetic amines on the synaptosomal transport of noradrenaline, dopamine and 5-hydroxytryptamine. Eur. J. Pharmacol. 41, 133–143.
Reavill, C., Stolerman, I.P., 1987. Interaction of nicotine with dopaminergic mechanisms assessed through drug discrimination and rotational behaviour in rats. J. Psychopharmacol. 1, 264–273.
Reavill, C., Stolerman, I.P., 1990. Locomotor activity in rats after administration of nicotinic agonists intracerebrally. Br. J. Pharmacol. 99, 273–278.
Reid, M.S., Ho, L.B., Berger, S.P., 1996. Effects of environmental conditioning on the development of nicotine sensitization: behavioral and neurochemical analysis. Psychopharmacology 126 (4), 301–310.
Robbins, T.W., 1975. The potentiation of conditioned reinforcement by psychomotor stimulant drugs: DA test of Hill's hypothesis. Psychopharmacology 45, 103–114.
Robbins, T.W., Koob, G.F., 1980. Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. Nature 285, 409–412.
Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Rev. 18, 247–291.
Rose, J.E., Corrigall, W.A., 1997. Nicotine self-administration in animals and humans: similarities and differences. Psychopharmacology 130 (1), 28–40.
Rosecrans, J.A., 1989. Nicotine as a discriminative stimulus: a neurobiobehavioral approach to studying central cholinergic mechanisms. J. Subst. Abuse Treat. 1, 287–300.
Russell, M.A.H., 1990. Nicotine intake and its control over smoking. In: Wonnacott, S., Russell, M.A.H., Stolerman, I.P. (Eds.), Nicotine Psychopharmacology: Molecular, Cellular, and Behavioural Aspects. Oxford Univ. Press, New York, pp. 374–427.
Salamone, J.D., 1992. Complex motor and sensorimotor function of striatal and accumbens dopamine: involvement in instrumental behavior processes. Psychopharmacology 107, 160–174.
Salamone, J.D., 1994. The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. Behav. Brain Res. 61, 117–133.

Sanger, D.J., 1986. Drug taking as adjunctive behavior. In: Goldberg, S.A., Stolermans, J. (Eds.), Behavioural Analysis of Drug Dependence. Academic Press, New York, pp. 123–160.

Saulskaya, N., Marsden, C.A., 1995. Conditional dopamine release: dependence upon *N*-methyl-D-aspartate receptors. Neuroscience 67, 57–63.

Schechter, M.D., Meehan, S.M., 1992. Further evidence for the mechanisms that may mediate nicotine discrimination. Pharmacol. Biochem. Behav. 41, 807–812.

Schechter, M.D., Meehan, S.M., 1993. Dopaminergic mediation of the stimulant generalization of nicotine. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 17, 835–845.

Schilström, B., Nomikos, G.G., Nisell, M., Hertel, P., Svensson, T.H., 1998a. *N*-methyl-D-aspartate receptor antagonism in the ventral tegmental area diminishes the systemic nicotine-induced dopamine release in the nucleus accumbens. Neuroscience 82, 781–789.

Schilström, B., Svensson, H.M., Svensson, T.H., Nomikos, G.G., 1998b. Nicotine and food induced dopamine release in the nucleus accumbens of the rat: putative role of $\alpha 7$ nicotinic receptors in the ventral tegmental area. Neuroscience 85, 1005–1009.

Schultz, W., Apicella, P., Ljungberg, T., 1993. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J. Neurosci. 13, 900–913.

Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.

Setlow, B., McGaugh, J.L., 1998. Sulpiride infused into the nucleus accumbens post-training impairs memory of spatial water maze training. Behav. Neurosci. 112, 603–610.

Singer, G., Oei, T.P., Wallace, M., 1982a. Schedule-induced self-injection of drugs. Neurosci. Biobehav. Rev. 6, 77–83.

Singer, G., Wallace, M., Hall, R., 1982b. 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.

Sorenson, E.M., Shiroyama, T., Kitai, S.T., 1998. Postsynaptic nicotinic receptors on dopaminergic neurons in the substantia nigra pars compacta of the rat. Neuroscience 87, 659–673.

Stolerman, I.P., 1987. Psychopharmacology of nicotine: stimulus effects and receptor mechanisms. In: Iversen, L.L., Iversen, S.D., Snyder, S.H. (Eds.), Handbook of Psychopharmacology Vol. 19 Plenum, New York, pp. 421–465.

Stolerman, I.P., 1992. Drugs of abuse: behavioural principles, methods and terms. Trends Pharmacol. Sci. 13, 170–176.

Stolerman, I.P., 1999. Interspecies consistency in the behavioural pharmacology of nicotine dependence. Behav. Pharmacol. 10, 559–580.

Stolerman, I.P., Garcha, H.S., Pratt, J.A., Kumar, R., 1984. Role of training dose in discrimination of nicotine and related compounds by rats. Psychopharmacology 84 (3), 413–419.

Svensson, T.H., Mathe, J.M., Nomikos, G.G., Schilstrom, B., 1998. Role of excitatory amino acids in the ventral tegmental area for central actions of non-competitive NMDA-receptor antagonists and nicotine. Amino Acids 14, 51–56.

Swanson, L.W., Simmons, D.M., Whiting, P.J., Lindstrom, J., 1987. Immunohistochemical localization of neuronal nicotinic receptors in the rodent central nervous system. J. Neurosci. 7, 3334–3342.

Tanda, G., Carboni, E., Frau, R., Di Chiara, G., 1994. Increase of extracellular dopamine in the prefrontal cortex: a trait of drugs with antidepressant potential? Psychopharmacology 115, 285–288.

Tanda, G., Di Chiara, G., 1998. A dopamine–μ_1 opioid link in the rat ventral tegmentum shared by palatable food (Fonzies) and non-psychostimulant drugs of abuse. Eur. J. Neurosci. 10, 1179–1187.

Tanda, G., Pontieri, F.E., Di Chiara, G., 1997a. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ_1 opioid receptor mechanism. Science 276, 2048–2050.

Tanda, G., Pontieri, F.E., Frau, R., Di Chiara, G., 1997b. Contribution of noradrenaline carrier to the increase of extracellular dopamine in the rat prefrontal cortex by amphetamine and cocaine. Eur. J. Neurosci. 9, 2077–2085.

Taylor, J.R., Robbins, T.W., 1986. 6-Hydroxydopamine lesions of the nucleus accumbens, but not of the caudate nucleus, attenuate enhanced responding with reward-related stimuli produced by intra-accumbens D-amphetamine. Psychopharmacology 90, 390–397.

Thornton, J.C., Dawe, S., Lee, C., Capstick, C., Corr, P.J., Cotter, P., Frangou, S., Gray, N.S., Russell, M.A.H., Gray, J.A., 1996. Effects of nicotine and amphetamine on latent inhibition in human subjects. Psychopharmacology 127, 164–173.

Tiffany, S.T., 1990. A cognitive model of drug urges and drug use behavior: role of automatic and nonautomatic processess. Psychol. Rev. 97, 147–168.

Vezina, P., Hervé, 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.

Wada, E., McKinnon, D., Heinemann, S., Patrick, J., Swanson, L.W., 1990. The distribution of mRNA encoded by a new member of the neuronal nicotinic acetylcholine receptor gene family ($\alpha 5$) in the rat central nervous system. Brain Res. 526, 45–53.

Wada, E., Wada, K., Boulter, J., Deneris, E., Heineman, S., Patrick, J., Swanson, L.W., 1989. Distribution of alpha2, alpha3, alpha4, and beta2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. J. Comp. Neurol. 284, 314–335.

Walter, S., Kuschinsky, K., 1989. Conditioning of nicotine effects on motility and behaviour in rats. Naunyn-Schmiedeberg's Arch. Pharmacol. 339 (1–2), 208–213.

Weiner, I., 1990. Neural substrates of latent inhibition: the switching model. Psychol. Bull. 10, 442–461.

White, N.M., Viaud, M.D., 1991. Localized intracaudate dopamine D2 receptor activation during the post-training period improves memory for visual or olfactory conditioned emotional responses in the rat. Behav. Neural Biol. 55, 255–269.

Wise, R.A., 1982. Neuroleptics and operant behavior: the anhedonia hypothesis. Behav. Brain Sci. 5, 39–87.

Wise, R.A., Leone, P., Rivest, P., Leeb, K., 1995a. Elevations of nucleus accumbeans dopamine and DOPAC levels during intravenous heroin self-administration. Synapse 21, 140–148.

Wise, R.A., Newton, P., Leeb, K., Burnette, B., Pocock, D., Justice, J.B. Jr., 1995b. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. Psychopharmacology 120, 10–20.

Wolterink, G., Phillips, G., Cador, M., Donselaar-Wolterink, I., Robbins, T.W., Everitt, B.J., 1993. Relative roles of ventral striatal D1 and D2 dopamine receptors in responding with conditioned reinforcement. Psychopharmacology 110, 355–364.

Young, A.M.J., Joseph, M.H., Gray, J.A., 1993. Latent inhibition of conditioned dopamine release in rat nucleus accumbens. Neuroscience 54, 5–9.