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Review

Drug addiction as dopamine-dependent associative learning disorder

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Abstract

Natural rewards preferentially stimulate dopamine transmission in the nucleus accumbens shell. This effect undergoes adaptive changes (one-trial habituation, inhibition by appetitive stimuli) that are consistent with a role of nucleus accumbens shell dopamine in associative reward-related learning. Experimental studies with a variety of paradigms confirm this role. A role in associative stimulus–reward learning can provide an explanation for the extinction-like impairment of primary reinforcement that led Wise to propose the 'anhedonia hypothesis'. Addictive drugs share with natural rewards the property of stimulating dopamine transmission preferentially in the nucleus accumbens shell. This response, however, in contrast to that to natural rewards, is not subjected to one-trial habituation. Resistance to habituation allows drugs to activate dopamine transmission in the shell non-decrementally upon repeated self-administration. It is hypothesized that this process abnormally strengthens stimulus-drug associations thus resulting in the attribution of excessive motivational value to discrete stimuli or contexts predictive of drug availability. Addiction is therefore the expression of the excessive control over behaviour acquired by drug-related stimuli as a result of abnormal associative learning following repeated stimulation of dopamine transmission in the nucleus accumbens shell.

Keywords: Dopamine; Addiction; Reward; Reinforcement; Self-administration; Learning; Incentive motivation

1. Drug reward and drug addiction

The self-administration of drugs outside a specific therapeutic indication and a professional prescription is probably as old as human culture and civilization and testifies that drugs serve as positive reinforcers (Johanson, 1978). On the other hand, the property of eliciting pleasurable feelings also indicates that drugs are indeed rewarding. Rewarding properties of drugs do not necessarily consist of sheer sensations of pleasure like the ''high'' or the ''rush'' typical of i.v. amphetamine and heroin or of inhaled crack (cocaine base) but can take milder forms of hedonia, like tension relief, reduction of fatigue, increased arousal, improvement of performance etc. These positive actions, can explain, per se, why drugs are used but not why they are abused. In particular, drug reward cannot fully account for drug addiction, a condition characterized by compulsive, relapsing drug use and focusing of motivated behaviour on drugs to the exclusion of alternative goals and in the face of familiar, social and medical problems.

Clearly, the rewarding properties of drugs, per se, at least as we understand them from their comparison with conventional rewards, do not justify the behavioural abnormalities associated to their use. One might argue that it is the specific modality by which drug reward takes place that makes the substantial difference with conventional reward; in fact, while conventional rewards act primarily as sensory stimuli, drugs act directly into the brain where they distribute from the plasma compartment. Although this is certainly a differential property of conventional and drug rewards it is unlikely to be, per se, the basis of the addictive properties of drugs. Caffeine, for example, a drug provided with rewarding properties, testified by the choice of millions of drinkers of caffeine-containing beverages, is not listed among addictive drugs and may not be addictive although can produce physical dependence after heavy chronic use (American Psychiatric Association, 1994).

While not sufficient, the rewarding properties of drugs are nonetheless necessary for their addictive liability for at least two reasons: first, drug reward, by promoting drug self-administration, is instrumental for repeated drug exposure, a necessary condition for addiction to develop; second, the rewarding properties of drugs are necessary for attributing, by an associative learning mechanism, positive

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motivational value to stimuli that predict drug availability and act as powerful incentives of drug-seeking behaviour.

Accordingly, drug addiction can be conceptualized as a disorder of motivation characterized by an excessive control over behaviour exerted by drugs through the acquisition of secondary, conditioned stimuli that act as incentives of drug-taking behaviour (Di Chiara, 1998). This view, although not new (Wikler, 1973; Goldberg, 1976; Stewart et al., 1984; Childress et al., 1988; O'Brien et al., 1992; Robinson and Berridge, 1993), is at variance with the traditional view of addiction as an homeostatic behaviour intended to maintain a new state induced by chronic drug exposure (Himmelsbach, 1943; Koob et al., 1989).

2. Dependence theories of drug-addiction

Early theories, by referring to opiate addiction as a model, placed major emphasis on physical dependence as a factor of drug addiction (Himmelsbach, 1943). More recent formulations, apart from providing a theory for the mechanism of tolerance and dependence (opponent process theory) (Solomon, 1977), have moved the emphasis from physical dependence to motivational dependence and to withdrawal-induced anhedonia and dysforia as motivational factors of drug addiction; this state, by a negative reinforcing mechanism, would maintain drug self-administration (Koob et al., 1989, 1997). The advantage of this modern version over early physical dependence theories is that motivational dependence, as assayed by electrical self-stimulation behaviour in animals (Markou and Koob, 1991), has the properties of a factor common to different classes of drugs while physical dependence widely differs, as judged from the phenomenology of physical abstinence, from one drug class to the other.

Although it is difficult to negate that drug dependence plays a role in drug addiction, this is unlikely to be necessary nor sufficient. This assumption is based on the fact that relapse of drug use takes place also after long periods of abstinence, when dependence is likely to have worn off, and that detoxification and recovery from a dependence state does not prevent relapse of drug abuse. In fact, drug-seeking takes place in spite of full detoxification and even under a full methadone maintenance regimen (Horns et al., 1975; Bell et al., 1990; Loimer and Schmid, 1992; De Vos et al., 1996).

3. Role of drug-related stimuli

It is a basic tenet of our hypothesis that the addictive properties of drugs are related to their property of stimulating dopamine transmission in the shell of the nucleus accumbens (Di Chiara, 1998). Drugs share this property with conventional reinforcers but this effect is not subjected to habituation upon repeated drug exposure as instead is the case of conventional reinforcers. We hypothesize that the repetitive, non-decremental stimulation of dopamine transmission induced by drugs in the nucleus accumbens shell abnormally strengthens stimulus–drug associations (reward-related learning). By this mechanism stimuli predictively associated to drugs are attributed excessive motivational value, thus becoming capable of controlling behaviour in that dominant and exclusive manner typical of addiction.

4. Addictive drugs stimulate dopamine transmission in the nucleus accumbens

Transcerebral brain microdialysis studies of the effects of drugs of abuse on dopamine transmission in the dorsal caudate–putamen and in the nucleus accumbens have shown that, not only psychostimulants like cocaine (Kuczenski and Segal, 1992) and amphetamine (Carboni et al., 1989) but also narcotic analgetics (Di Chiara and Imperato, 1988b), nicotine (Imperato et al., 1986; Brazell et al., 1990), ethanol (Imperato and Di Chiara, 1986) and phencyclidine (Carboni et al., 1989) stimulate dopamine transmission in the nucleus accumbens (Di Chiara and Imperato, 1988a), the main area of the ventral striatum (Heimer and Wilson, 1975). The mechanism by which addictive drugs stimulate dopamine transmission is different depending on the drug class they belong to. Psychostimulant (cocaine, amphetamine) and non-psychostimulant drugs (narcotics, nicotine, ethanol, Δ^9tetrahydrocannabinol) differ for the fact that while psychostimulants inhibit the firing activity of dopamine neurons indirectly by increasing dopamine onto somatodendritic or terminal dopamine autoreceptors, non-psychostimulants increase the firing activity of dopamine neurons.

A comparison of the action of addictive drugs on in vivo dopamine transmission in the nucleus accumbens and in the dorsal caudate–putamen showed that their stimulation was preferential in the nucleus accumbens. This preferential stimulation of terminal dopamine transmission in the nucleus accumbens is associated in the case of non-psychostimulant drugs (narcotic analgetics, ethanol, nicotine) to a preferential stimulation of the firing activity of dopamine neurons of the ventral tegmental area as compared to pars compacta (Matthews and German, 1984; Gessa et al., 1985; Mereu et al., 1987). Therefore, the preferential effect of non-psychostimulant drugs on dopamine transmission in the nucleus accumbens as compared to the dorsal caudate–putamen appears to be due to a preferential stimulation of the firing activity of dopamine neurons projecting from the ventral tegmental area to the ventral striatum as compared to dopamine neurons projecting from the substantia nigra pars compacta to the dorsal striatum. A lower efficiency of dopamine reuptake in the nucleus accumbens as compared to the dorsal striatum has

been suggested to be the basis for the preferential effect of cocaine in the nucleus accumbens (Cass et al., 1992).

4.1. Localization of dopamine stimulant effects of addictive drugs to the nucleus accumbens ''shell''

Studies of the effect of amphetamine on extracellular dopamine with concentric microdialysis probes vertically placed at different medio-lateral levels in the nucleus accumbens showed significant differences between the dorsal caudate–putamen and the medial but not the lateral part of the nucleus accumbens (Di Chiara et al., 1993a,b). On the basis of these observations, failure of some studies to observe differences in the dopamine stimulant effects of amphetamine between the nucleus accumbens and the dorsal caudate–putamen (Robinson and Camp, 1990; Kuczenski and Segal, 1992) was explained as due to differences in the sensitivity to amphetamine of dopamine projections to the medial and lateral nucleus accumbens (Di Chiara, 1991).

Indeed, histochemical and connectional studies have distinguished in the nucleus accumbens a ventro-medial ''shell'' and a dorso-lateral ''core''. On the basis of their input–output relationships, these two subdivisions have been assigned a different functional significance, the ''core'' being involved in motor functions and the ''shell'' being involved in emotion as a transition area of the extended amygdala (Alheid and Heimer, 1988; Heimer et al., 1991). In order to verify the possibility of shell/core differences in responsiveness of dopamine to drugs of abuse, rats were implanted with intravenous catheters and with concentric microdialysis probes aimed at the nucleus accumbens ''core'' of one side and at the ''shell'' of the other side (Fig. 1) and the changes in dopamine transmission were studied after various drugs given i.v. at unitary doses known from the literature to maintain self-administration behaviour in the rat. Calbindin immunohistochemistry was utilized to distinguish ''shell'' from ''core'' in the histological verification of probe location. These studies (Pontieri et al., 1995, 1996; Tanda et al., 1997a) showed that non-psychostimulant drugs (including morphine, heroin (Fig. 2), nicotine (Fig. 3) and Δ^9tetrahydrocannabinol (Fig. 2), at each of the two doses tested, increased dialysate dopamine selectively in the nucleus accumbens shell. Cocaine showed a selective effect in the shell at lower doses and a preferential one at higher doses (Fig. 4). Amphetamine showed a preferential effect in the shell at lower doses but at higher doses the effect was similar in the shell and in the core. Similar observations were made for morphine and amphetamine given subcutaneously and for cocaine given intraperitoneally (Cadoni and Di Chiara, 1999). More recently, a preferential effect of amphetamine in the anterior shell has been reported after local intracerebral infusion (Heidbreder and Feldon, 1998). Similar findings have been reported by Barrot et al. (1998) for morphine and cocaine.

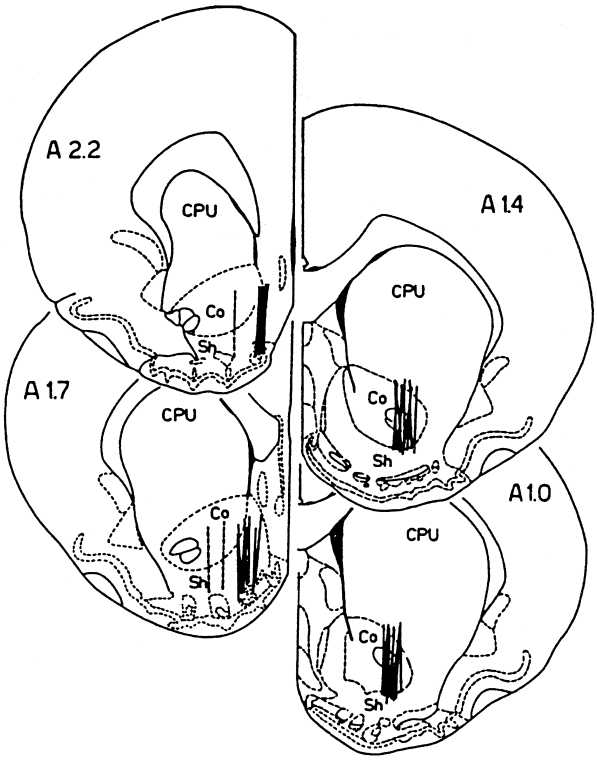

Fig. 1. Localization of dialysis probes (dialysing portion) within the nucleus accumbens (Nac) and their relationship with ''shell'' and ''core''. Dashed lines indicate probes aimed at the ''shell'' but residing in the ''core''. CPU = caudate putamen; Co = 'core'; Sh = 'shell' of the nucleus accumbens. Reproduced from Pontieri et al. (1995) with permission by *The National Academy of Sciences, USA.*

In parallel studies with 2 deoxyglucose autoradiography it was also shown that nicotine, morphine, cocaine and amphetamine activate at low doses energy metabolism selectively in the nucleus accumbens shell, indicating that stimulation of dopamine transmission in this area by drugs of abuse increases the activity of intrinsic and afferent neural input (Pontieri et al., 1994; Orzi et al., 1996).

4.2. 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 (Tanda et al., in preparation). The effect of caffeine on dopamine 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

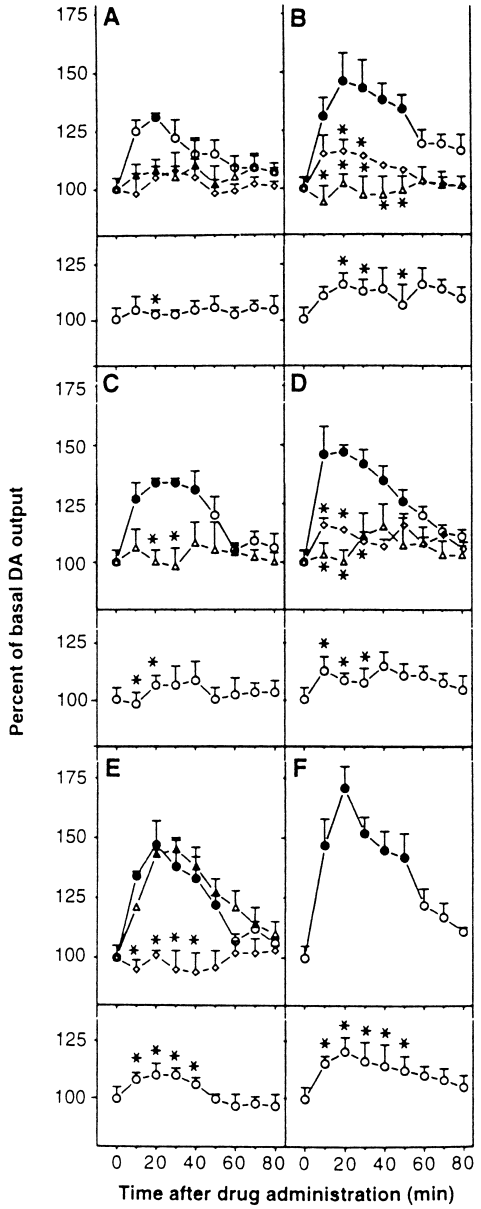

Fig. 2. Effect of intravenous Δ^9-THC, WIN55212-2, and heroin on dialysate dopamine in the shell (upper panels) and core (lower panels) of the nucleus accumbens, (A and B) Δ^9-THC doses of 0.15 and 0.30 mg/kg i.v.; (C and D) WIN55212-2 doses of 0.15 and 0.30 mg/kg i.v.; and (E and F) heroin doses of 0.018 and 0.030 mg/kg i.v. Rats were pretreated with saline (circles) or SR141716-A (triangles) (1 mg/kg s.c.) or with naloxone (diamonds) (0.1 mg/kg i.p.). Results are means ± S.E.M. of the amount of dopamine in 10-min dialysate samples, expressed as percent of basal values. Solid symbols: $P < 0.05$ compared with basal values. $^*P < 0.05$ compared with the corresponding value obtained in the shell of saline-pretreated controls. Reproduced from Tanda et al. (1997a) with permission by *Science*.

dopamine transmission in the nucleus accumbens shell is consistent with a role of nucleus accumbens shell dopamine in the addictive properties 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). GBR 12909, 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 block-

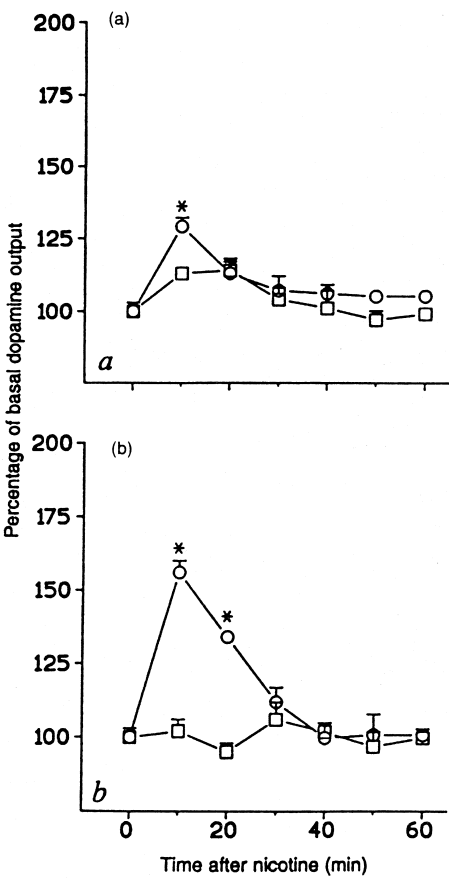

Fig. 3. Effect of i.v. administration of nicotine on dopamine (DA) output in dialysates from the 'shell' (●) and 'core' ( ) subdivisions of the nucleus accumbens in the rat. Percentage variations in dopamine output were produced by nicotine (free base) at 0.05 mg/kg (a) and 0.050 mg/kg (b). Post-hoc analysis indicated a significant increase over basal values in the shell at 10 and 20 min after administration of 0.05 mg/kg nicotine and at 10 min after administration of 0.025 mg/kg nicotine (*, $p < 0.05$ in the 'shell' compared with basal values and to the corresponding values in the 'core'). Reproduced from Pontieri et al. (1996) with permission by *Nature*.

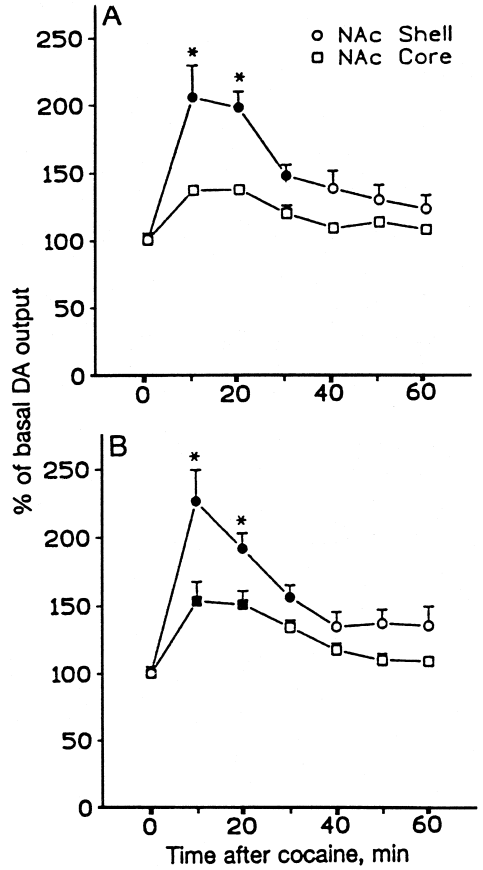

Fig. 4. Effect of i.v. cocaine on dopamine (DA) output in dialysates from 'shell' and 'core' subdivision of the nucleus accumbens (NAc) of freely-moving rats. (A) Cocaine, 0.5 mg/kg i.v. (B) Cocaine, 1.0 mg/kg i.v. Results are means ± S.E.M. of the amount of dopamine in each sample expressed as the percent of basal values. Basal values expressed as fmol per sample were as follows: 'shell', 64 ± 7; 'core', 60 ± 6 (means ± S.E.M. of eight rats). Filled symbols indicate a significant increase over basal levels ($p < 0.05$; Tukey's test). Reproduced from Pontieri et al. (1995) with permission by the National Academy of Sciences, USA. $^{*}p < 0.05$ compared with the corresponding sample in the 'core'. Reproduced from Pontieri et al. (1995) by permission of *The National Academy of Sciences, USA.*

ade 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 10 000 times difference in the ratio of noradrenaline terminals to dopamine terminals in the prefrontal cortex as compared to the nucleus accumbens (Palkovits, 1979) and by the high efficiency (4 times more than towards noradrenaline 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 of the lack of addictive liability or psychostimulant properties of antidepressants, that increase dopamine in the PFCX 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).

These observations indicate that the property of stimulating dopamine transmission in the nucleus accumbens shell is not secondary to generic motivational stimulus properties or to psychostimulant properties of addictive drugs.

The interpretation of the role of the stimulant effect of drugs of abuse on dopamine transmission in drug addiction is necessarily influenced by our understanding of the role of dopamine in behaviour motivated by non-drug rewards.

5. Motivational stimuli

Dopamine has been traditionally involved in motivation. Motivation is the process by which organisms respond to stimuli in relation to their value for survival. This value can be positive or negative depending on the predicted consequences, beneficial or harmful of the stimuli. Positive stimuli, in turn, can be either appetitive or consummatory depending on the type of behaviour they elicit: flexible patterns of search and approach to the reward (appetitive behaviour) or fixed patterns of consumption of the reward for the utilization of its biological resources (consummatory behaviour) (Konorski, 1967). Motivational stimuli are either primary or secondary depending on the fact that their value is genetically predetermined or acquired by learning of their predictive association with primary stimuli. Associative learning is therefore the mechanism by which otherwise neutral stimuli acquire motivational value; this value is expressed by the property of eliciting simple approach responses if stimuli are attributed a positive value or behavioural inhibition and freezing if attributed a negative value (Schneirla, 1959).

The above one, however, is only one aspect of the complex process by which stimuli generate responses useful for survival. Thus, motivation involves the possibility that organisms actively influence by their behaviour the occurrence of biologically significant stimuli (operant or instrumental behaviour). Traditionally, depending on the fact that responding has the consequence of enhancing or reducing the occurrence or the strength of a motivational stimulus, reinforcement has been distinguished into positive and negative. However, negative reinforcement can be easily reduced to positive reinforcement if referred to the occurrence of safety stimuli or events that, by allowing avoidance of a punisher, have a positive value (Mackintosh, 1974).

Instrumental learning is the process by which the subject learns to actively control the occurrence of biologically significant events. This learning involves learning of stimulus-reward as well as stimulus–response contingencies (Rescorla and Solomon, 1967). For example, even in primary drug self-administration, a stimulus–reward association is likely to be first established towards discriminative drug cues which are than utilized for establishing a stimulus–response relationship.

It has been proposed that response emission is controlled by an explicit/declarative expectancy of stimulus outcome involving the formation of a cognitive representation of the motivational value of the stimulus by reexposure to it (incentive learning) following its pavlovian association with the primary stimulus or state (Dickinson and Balleine, 1995). Following exhaustive training, stimulus–response relationships can be strengthened to such an extent (habit learning) that responding becomes relatively independent from outcome (Dickinson and Balleine, 1995).

6. Rewards, reinforcers, incentives

When referring to drug abuse and addiction terms like reward, reinforcer and incentive are often used interchangeably. However, while it is true that rewards are also reinforcers, reinforcers are not necessarily rewards. Rewards are positive stimuli with primary motivational value as they predict events useful for survival without requiring an associative learning process. From a psychological point of view, the term reward involves the notion of hedonia and pleasure, an emotional, affective quality that can be verbally expressed to the extent it corresponds to a conscious mental state. In animals, one can only infer the hedonic properties of rewards from their impact on behaviour. Given the fact that the hedonic properties of rewards are experienced during the consummatory phase of motivated behaviour, the evaluation of their hedonic impact in animals is made on the basis of the behavioural features of their consumption (e.g., taste reactivity paradigm) (Grill and Norgren, 1978).

In addition to the notion of pleasure, the term reward includes, when it refers to natural stimuli, the notion of satiety. Satiety is part of an homeostatic mechanism by which the motivational value of rewards is reduced once the need state which augmented their motivational properties has been corrected by their consumption. This means that the biological properties of rewards, while not part of their stimulus properties, are nonetheless essential for the maintenance of their rewarding properties (Le Magnen, 1969).

The terms *reinforcer* and *reinforcement* can have different meanings. Although Skinner (1935) is commonly credited for introducing the term reinforcer, Pavlov had already utilized this term in a different context (Pavlov, 1927). In general, reinforcers are stimuli that strengthen the association of events to which they follow i.e. upon which they are contingent. Depending on the fact that reinforced events are stimuli or responses, two types of reinforcement can be distinguished: pavlovian or stimulus-reinforcement, whereby a stimulus predictively associated with a reinforcer acquires the response-eliciting properties of the reinforcer, and response-reinforcement, whereby the emission of responses upon which the reinforcer is contingent is specifically increased (instrumental or operant reinforcement) (Skinner, 1935, 1937).

The term *incentive* (Bolles, 1972; Bindra, 1974) is currently utilized interchangeably with that of reinforcer both in the pavlovian and skinnerian sense. In fact, incentive theorists have interpreted operant-reinforcement in terms of pavlovian stimulus-reinforcement (Bindra, 1978). Moreover, an instrumental component is present also in a typical incentive response as conditional approach (Holland and Straub, 1979). Therefore, the responses elicited by incentives are either instrumental to the occurrence of the stimulus itself or simply contingent upon it (i.e., that follow it).

7. Dopamine and reward

The first proposal of a unique relationship between dopamine and reward was provided by Wise following a series of studies showing that neuroleptics produce delayed, intra-session impairment of operant reinforcement maintained by natural reinforcers (food, water) as well as by intracranial self-stimulation and by drugs (Wise, 1982). The delayed character of the impairment and its resemblance with extinction led Wise to conclude that neuroleptics impair specifically primary reinforcement independently from an action on performance. Indeed, differences between the action of extinction and of neuroleptics on primary reinforcement have been noted (Salamone et al., 1997) but can be explained as the result of additional actions of neuroleptics superimposed to an action on primary reinforcement.

After almost 25 years, the original conclusion that neuroleptics impair primary reinforcement is still valid, being consistent with a large body of evidence on a variety of paradigms (Beninger, 1983; Ettenberg, 1989). Particularly relevant to the interpretation of the mechanism of the extinction-like effect of neuroleptics are the studies by Ettenberg et al., showing that neuroleptics impair the ability of rewards to reinstate responding reduced by extinction (Horvitz and Ettenberg, 1988; Ettenberg, 1990; Ettenberg and Horvitz, 1990; Ettenberg et al., 1996; McFarland and Ettenberg, 1997). This response-reinstating effect of rewards is exactly what was meant by Pavlov (1927) with the term ‘reinforcement’ as the ability of an unconditioned stimulus to strengthen the conditional response-eliciting properties of a stimulus that had been weakened by extinction. Therefore, the observations of

Ettenberg et al. show that neuroleptics can selectively impair pavlovian stimulus-reinforcement.

Wise (1982) further interpreted the extinction-like effect of neuroleptics as due to an impairment of the pleasurable effects of rewards (anhedonia) and hypothesized that dopamine mediates the hedonic properties of rewards. The 'anhedonia hypothesis' was soon replaced by Wise himself with an incentive-motivational hypothesis following the observation that neuroleptics impair responding to conditional stimuli (secondary reinforcement) independently from reinforcement by the reward (Wise, 1985). However, the action of neuroleptics on secondary reinforcement might be quite distinct from that on primary reinforcement (see below).

Given the fact that hedonia is a mental state and that the anhedonia hypothesis was meant to be tested in man (Wise, 1985), the obvious and major difficulty of the anhedonia hypothesis has been its testing in animals. Nonetheless a role of dopamine in the hedonic impact of rewards has been investigated by the taste reactivity paradigm. In this paradigm, the species-specific repertoire in response to appetitive or aversive taste stimuli is recorded and scored (Grill and Norgren, 1978). Dopamine receptor antagonists (both D_1 and D_2) and 6-OH dopamine lesions of dopamine terminals in the nucleus accumbens consistently failed to impair hedonic reactions (Peciña et al., 1997; Berridge and Robinson, 1998).

The anhedonia hypothesis has probably generated an equal amount of interest as of skepticism (Salamone et al., 1997). However, when discussing the effect of neuroleptics, in order to avoid throwing away the child (the effect of neuroleptics on primary reinforcement) together with the water (the effect of neuroleptics on hedonia), a distinction should be made between reinforcing and hedonic properties of rewards. The reason for this is that hedonia is only one aspect of rewards and, eventually, not the most useful one from an operational point of view. Thus, the essential function of rewards may not be that of inducing pleasure but of establishing a cause–effect relationship (initially implicit, later made explicit by re-exposure to the stimulus) between stimuli and events provided of biological value in order to make them reliable predictors of events and outcomes useful for survival. This is exactly what is meant by reward reinforcement. Neuroleptics might impair this process independently from hedonia. If such distinction between primary reinforcement and hedonia is made, rejection of an anhedonia hypothesis would be still compatible with acceptance of a reinforcement-impairment hypothesis of the action of neuroleptics.

7.1. Dopamine and drug reward

The fact that direct as well as indirect dopamine receptor agonists have unconditional incentive, approach-eliciting and primary reinforcing properties justifies the notion that pharmacological stimulation of dopamine transmission by drugs like amphetamine and cocaine (psychostimulants) is rewarding (Wise and Bozarth, 1987; Di Chiara, 1995). Moreover, it is difficult to dispute the hedonic quality of the cocaine and amphetamine ''rush'', that addicts compare to sexual orgasm and exhaustively chase by binge taking (Fischman, 1989). Some authors, however, have noted that dopamine receptor blockers affect ''wanting'' (incentive state) rather than ''liking'' (hedonia) in response to psychostimulants and have utilized this argument to suggest that dopamine mediates the incentive but not the hedonic properties of these drugs (Berridge and Robinson, 1998). This again would leave hedonia out of the dopamine-dependent properties of psychostimulants; however, before considering this possibility one should ask if the dopamine-receptor antagonists utilized in these experiments were adequate to fully block the dopamine-mediated actions of psychostimulants. The fact that preferential D_2-like receptors antagonists were utilized in these studies (Brauer and De Wit, 1996, 1997; Brauer et al., 1997) leaves open the possibility of a role of dopamine D_1-receptors and suggests that dopamine D_1-receptor antagonists should be also tested alone or in conjunction with classic neuroleptics.

8. Dopamine, incentive motivation and secondary reinforcement

Among the behavioural roles attributed to dopamine probably the most popular one is the incentive/activational one (see Berridge and Robinson, for review). This role is directly derived from incentive-motivational theories (Bolles, 1972; Bindra, 1974) and from the role attributed by Mogenson et al. (1980) to the nucleus accumbens as an interface between motivation and action.

The hypothesis of a role of dopamine in incentive motivation assumes that incentive stimuli are able to physically release dopamine in terminal dopamine areas. This action would amplify or enable the expression of the response eliciting properties of incentive stimuli (Berridge, 1996).

This hypothesis is based on experimental as well as correlative evidence. Early evidence derives from the observation that neuroleptics impair secondary reinforcement even before the presentation of the reward (Phillips and Fibiger, 1979; Gray and Wise, 1980) as well as appetitive/preparatory but not consummatory behaviour rewarded by conventional stimuli (Blackburn et al., 1987). Since appetitive/preparatory behaviour is thought to be a response to secondary incentive stimuli this effect would be consistent with an impairment of incentive–motivation by neuroleptics.

An experimental evidence commonly taken in support of an incentive–motivational role of dopamine is the augmenting effect of amphetamine and of other psychostimulants on secondary reinforcement (Hill's effect) (Hill, 1970; Robbins, 1975; Beninger and Phillips, 1981) and their stimulant effects on forward locomotion (Wise and Bozarth, 1987). Finally, a role of dopamine in the action of incentives is apparently supported by in vivo monitoring and single unit recording studies showing phasic increases of dopamine in the nucleus accumbens and of unit activity in the mesencephalon following presentation of secondary reinforcers (see Section 6).

However, compelling evidence for a distinction between an incentive and a reinforcement role of dopamine has been provided by Ettenberg and coll. Thus, in a straight alley paradigm, dopamine receptor blockade fails to reduce the incentive (running the alley) properties 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).

The above distinction between incentive properties of stimuli and primary reinforcement is consistent with differences in the action of neuroleptics on primary versus secondary reinforcement and incentive responding (Franklin, 1978; Franklin and McCoy, 1979; Gallistel et al., 1982). This can be interpreted to signify that the extinction-like effect of neuroleptics and the impairment of incentive responding and secondary reinforcement are due to two distinct mechanisms related to two separate roles of dopamine in motivation and reward.

We hypothesize that the effect of neuroleptics on primary reinforcement is due to an action on the acquisition of pavlovian stimulus-reinforcement, i.e., on the associative learning mechanism by which the stimulus acquires and maintains its motivational value (stimulus–reward learning); instead, the action of neuroleptics on incentive responding and secondary reinforcement would be due to an action on activational aspects of behaviour necessary for motor expression not dissimilar from the role attributed by Mogenson et al. (1980) to the nucleus accumbens as an interface between motivation and action.

These two actions of neuroleptics, in turn, might be indicative of two distinct roles of dopamine in motivation: (1) in the acquisition of rewarding value by stimuli through an action on stimulus–reward learning; (2) in the expression of that value into a response (incentive responding, secondary reinforcement) and in strengthening of response habits (stimulus–reinforcement).

9. Dopamine and associative learning

A role of dopamine in associative learning related to pavlovian reinforcement provides an explanation of the extinction-like effect of neuroleptics on primary reinforcement. The problem, however, is to establish exactly which form of associative learning is impaired by neuroleptics.

A role of dopamine in simple stimulus-stimulus learning has been excluded on the basis of the failure of neuroleptics to impair stimulus discrimination learning as well as conditional emotional responses to stimuli paired to appetitive or aversive stimuli (Beninger, 1983). Recently, however, a role of dopamine in the nucleus accumbens in associative stimulus–stimulus learning has been proposed on the basis of microdialysis studies (Young et al., 1998); however, an alternative explanation of these results can be provided in terms of different sensory salience of simple versus compound stimuli.

Conditional aversive and appetitive stimuli acquired under the action of neuroleptics, when subsequently tested for their ability to elicit operant responding in the absence of the neuroleptic are differentially capable of inducing responses; thus, while aversively conditioned stimuli elicit appropriate responding, appetitively conditioned stimuli fail to do so (Beninger and Phillips, 1980, 1981; Beninger et al., 1980).

These observations suggest that dopamine is essential for a stimulus to acquire, by predictive association with a reward (stimulus–reward learning), motivational value, as expressed by the ability to act in a subsequent instrumental test as a positively reinforcing stimulus.

The impairment induced by neuroleptics does not involve the learning of emotional value as indicated by conditioned emotional responses, which are left intact by neuroleptic exposure (Beninger and Phillips, 1981), but only learning of the ability of the stimulus to acquire positive reinforcing properties on a subsequent neuroleptic-free test.

Given the relative specificity of neuroleptics for D_2 receptors and the existence of other dopamine receptor subtypes, the role of dopamine in learning may not be restricted to that on appetitive reward-related learning. In fact, studies with dopamine D_1-receptor antagonists seem to indicate a role of dopamine also in aversive learning.

Thus, in a place-conditioning paradigm, dopamine D_1-receptor antagonists reduce acquisition to the drug-conditioned compartment no matter if appetitive or aversive drugs are utilized (Acquas et al., 1989; Acquas and Di Chiara, 1994). Moreover, post-session intra-cerebral (intra-hypothalamic) administration of a dopamine D_1-antagonist in a conditioned taste aversion paradigm impairs learning (Caulliez et al., 1996).

A role of dopamine in consolidation of stimulus–reward associations has been reported by various studies. Thus, post-session infusion of D-amphetamine as well as a D_2/D_3 receptor agonist in the amygdala has been shown to increase the retention of stimulus–reward associations in an approach task but to be without effect on stimulus–response learning as expressed by the instrumental efficacy of the stimulus acting as a secondary reinforcer of a novel

task (Hitchcott et al., 1997a,b). This action of dopamine originates from the central amygdala (Hitchcott and Phillips, 1998), an area that has been assigned to the extended amygdala, which in turn bears strong relationships and homologies with the nucleus accumbens shell (Heimer et al., 1991).

10. Relationship of nucleus accumbens shell dopamine to rewarding stimuli

The role of dopamine in motivation can be inferred from correlative studies of the changes of dopamine transmission in specific brain areas elicited by motivational stimuli.

Among correlative studies much disagreement does exist between studies utilizing brain microdialysis and those utilizing voltammetry for the estimation of extracellular dopamine. In studies of water, food or drug responding, voltammetry studies have reported phasic *reductions* of extracellular dopamine in the nucleus accumbens associated to reward consumption or drug self-administration (Kiyatkin et al., 1993; Gratton and Wise, 1994; Kiyatkin and Gratton, 1994; Kiyatkin and Stein, 1996; Richardson and Gratton, 1996) while *elevations* of extracellular dopamine are consistently observed by microdialysis studies (see Young, 1994; Di Chiara, 1995; Westerink, 1995 for reviews). The difficulty in explaining these discrepancies by experimental differences raises the possibility that microdialysis and voltammetry differ in some intrinsic aspect related to quantitative or qualitative aspects of the molecular species being assayed.

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 and 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) (Figs. 5–7). 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 physically 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) (Fig. 7); 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 (Mark 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.

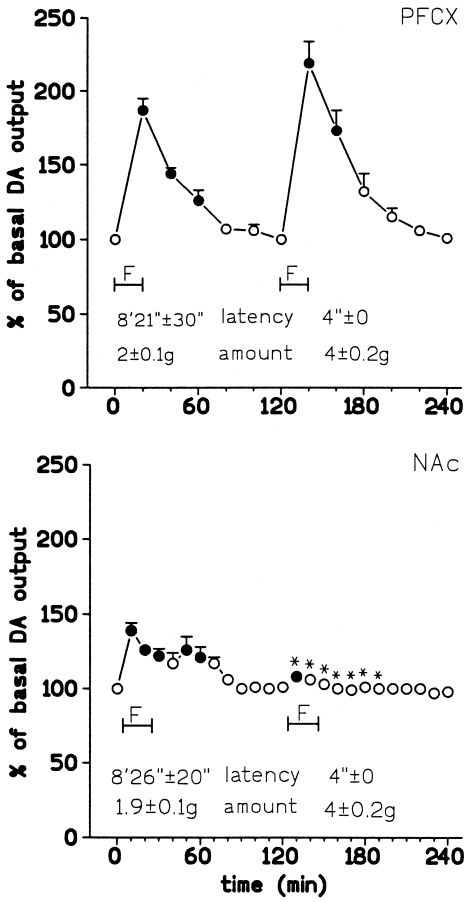

Fig. 5. Effect of repeated Fonzies (F) feeding during the same microdialysis session on dopamine (DA) output in dialysates from the prefrontal cortex (PFCX) (a) and the nucleus accumbens (NAc) (b). Latency to eat (s) and the amount of Fonzies eaten (g) are also indicated. Results are means ± S.E.M. of results obtained in at least four rats. Filled symbols, $p < 0.05$ in respect of basal values. $^{*}p < 0.05$ in respect of the previous Fonzies meal. Reproduced from Bassareo and Di Chiara (1997) with permission by *The Journal of Neuroscience*.

Voltammetry (chronoamperometric) studies with stearate coated electrodes have reported increases of dopamine in the nucleus accumbens core and shell in response to stimuli conditioned to conventional and drug reward (Richardson and Gratton, 1996; Di Ciano et al., 1998a,b). It is remarkable that in these studies conditional stimuli are as effective as cocaine or amphetamine in raising the dopamine signal (Di Ciano et al., 1998a). This is particularly notable if one considers that in microdialysis studies amphetamine at doses correspondent to those utilized in these voltammetry studies, increases dopamine by up to 10 or more times the basal values (Carboni et al., 1989; Kuczenski and Segal, 1992; Pontieri et al., 1995).

From microdialysis observations it appears that prefrontal cortex and nucleus accumbens core dopamine is stimulated by generic motivational stimuli either condi-

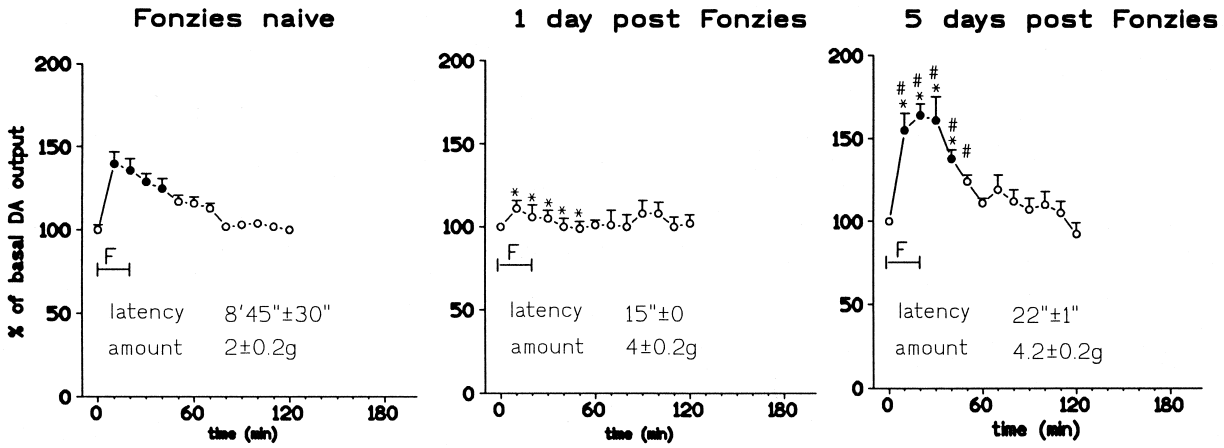

Fig. 6. Effect of previous Fonzies (F) feeding on dopamine (DA) output in dialysates from the nucleus accumbens (NAc). Three groups were compared, (a) naive, fed on Fonzies (b) 1 or (c) 5 days prior to the experiment. Latency to eat (s) and amount of Fonzies eaten to the experiment. Latency to eat (s) and amount of Fonzies eaten (g) are also indicated. Results are means ± S.E.M. of results obtained in at least four rats. Filled symbols, $p < 0.05$ in respect of basal values, $^{*}p < 0.05$ for the Fonzies naive rats; $^{\#}p < 0.05$ for the rats fed on Fonzies 1 day prior to the experiment. Reproduced from Bassareo and Di Chiara (1997) with permission by *The Journal of Neuroscience*.

tional 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, conditional stimuli.

10.1. Adaptive properties of dopamine responsiveness to motivational stimuli

The adaptive properties of dopamine responsiveness to motivational stimuli enables to further characterize the nature of dopamine responsiveness.

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); similarly, a 40 min pre-exposure to appetitive stimuli predictive of food inhibits 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 (Figs. 5–7).

The above changes observed in the in vivo dopamine transmission in response to motivational stimuli 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.

These results are at variance in many respects from those obtained by in vivo monitoring of dopamine transmission not only in the nucleus accumbens shell but also in the core and in the prefrontal cortex in response to primary and secondary food stimuli (Bassareo and Di Chiara, 1997, 1999). Thus, while dopamine units recorded extracellularly respond to secondary stimuli, no such property has been observed by microdialysis of dopamine in the nucleus accumbens shell. On the other hand, while in the experiments of Schultz et al. (1993, 1997), dopamine units repeatedly respond without habituation to stimuli, unless a new predictive stimulus is introduced, in microdialysis studies dopamine transmission in the nucleus accumbens shell undergoes habituation after a single exposure to a primary stimulus (Bassareo and Di Chiara, 1997).

At any rate, a direct comparison between unit recording and microdialysis studies is difficult due to the lack of some essential information. Thus, while microdialysis studies allow the study of the properties of dopamine transmission in specific terminal areas, this is not the case of single unit recording studies as those studies did not involve determination of the site of termination of the recorded units (Schultz et al., 1997).

Shifts in the phasic responsiveness of dopamine units from the reward to the conditional stimulus during learning of a conditional reinforcer have been interpreted in terms of a role of dopamine in signalling the unpredicted occurrence of a reward (Schultz et al., 1997). However, it has been pointed out that the responsiveness of dopamine units is not exclusive of rewards or appetitive stimuli as it extends to generically salient, novel stimuli (Redgrave et al., 1999). Therefore, the responsiveness of dopamine units might be simply secondary to the sensory or motivational salience of stimuli, either unconditioned or acquired as a result of a dopamine-independent learning. In particular, shifts in the responsiveness of dopamine units with learning might reflect the unique relationship with responding (motivational salience) acquired by the conditional stimu-

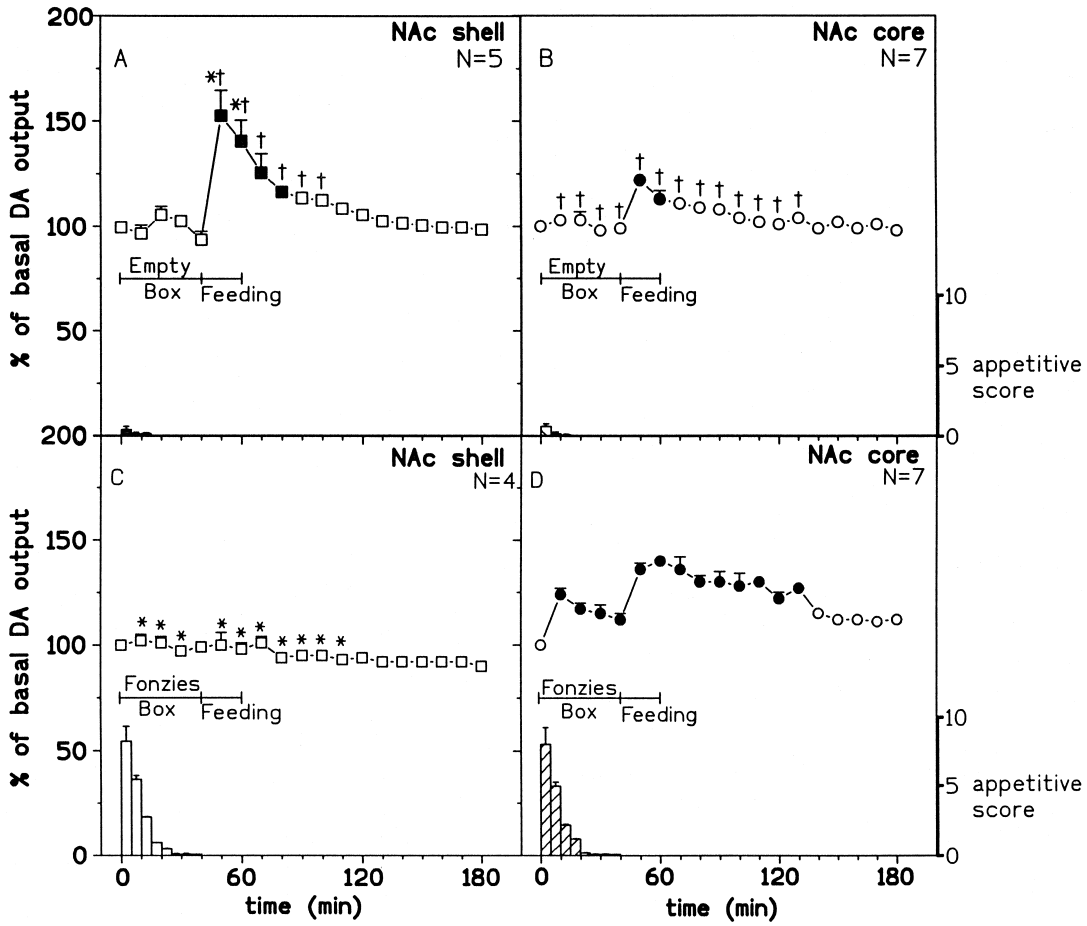

Fig. 7. Effect of neutral (empty box) or conditional food stimuli (Fonzies filled boz) and of Fonzies feeding on dialysate dopamine in the nucleus accumbens shell and core and on appetitive score. Results are means ± S.E.M. expressed as % of basal values. Basal values in fmoles dopamine/sample were: nucleus accumbens shell: 64 ± 6 (means ± S.E.M. of 9 rats); nucleus accumbens core: 60 ± 6 (means ± S.E.M. of 14 rats). Filled symbols: $p < 0.05$ with respect to basal values; *, $p < 0.05$ with respect to the corresponding value of the group implanted in the nucleus accumbens core (A vs. B and C vs. D); $p < 0.05$ with respect to the corresponding value of the group preexposed to Fonzies filled box (A vs. C and B vs. D). Fonzies (KP Snack foods, Germany) is a snack food made of corn flour, hydrogenated vegetable fat, cheese powder, salt and monosodium glutamate as taste enancer. Rats were fed ad libitum. Rats do not show appetitive responses to the smell of Fonzies placed inside a perforated opaque plastic box unless they learn the relationship between Fonzies smell and taste. Therefore, rats were fed on Fonzies 5 days before the experiment by placing 2 g of it in the home cage. Perforated cylindrical boxes were made of sky-blue plastic and were 8 cm in height and 6 cm in diameter. They were utilized either empty (A and B) or filled up with 8 g of Fonzies (C and D). In order to adapt the rats to the empty plastic box this was placed in their home cage for the whole day before probe implants. Reproduced from Bassareo and Di Chiara (1999) with permission by *Neuroscience*.

lus as a result of the prolonged training required for acquisition of dopamine responsiveness. From this point of view, the changes in the responsiveness of dopamine units would correspond to those observed by microdialysis in the prefrontal cortex and in the nucleus accumbens core, rather than in the nucleus accumbens shell (Bassareo and Di Chiara, 1997, 1999).

The properties of dopamine neurons as deduced from microdialysis studies are consistent with the possibility that dopamine plays different roles in a behaviour related to specific brain areas.

Specifically, the properties of dopamine responsiveness in the nucleus accumbens shell suggest a role in associative stimulus–reward learning. 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 to responding to unfamiliar, palatable tastes. Thus, release of dopamine in the nucleus accumbens by an unfamiliar palatable food might serve to associate food taste to its post-ingestive consequences. In this manner, depending on its outcome, the same taste can be accepted or rejected on a further encounter.

Instead, the properties of dopamine transmission in the nucleus accumbens core and in the prefrontal cortex are consistent with a role in the expression of motivation, in agreement with the notion of the nucleus accumbens as an interface between motivation and action (Mogenson et al., 1980).

10.2. Stimulation of dopamine transmission by aversive stimuli: primary or secondary?

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). This argument, however, in order to disprove a rewarding role of dopamine, has to imply that changes in dopamine transmission in the nucleus accumbens are primary to the motivational properties of the stimulus, i.e., that the stimulus depends for its aversive properties from release of dopamine or, to be explicit, that dopamine is aversive. If one applies this reasoning to β-endorphin it would sound as follows: β-endorphin has an algesic role (elicits pain) because is increased by painful stimuli. Obviously, no one makes this reasoning because it is known and accepted that β-endorphin is analgetic (reduces pain).

This indeed is not far from the case of dopamine. Thus, a primary increase of dopamine transmission in the nucleus accumbens induced by pharmacological means has rewarding, incentive and positively reinforcing properties (Di Chiara, 1995). This is just the opposite of what one would predict for an aversive stimulus. Therefore, stimulation of dopamine transmission by aversive stimuli is more likely to be a secondary change with adaptive significance. This does not mean necessarily that dopamine is rewarding but at least that plays an anti-aversive role, that is, the function of protecting against the negative consequences of aversive stimuli.

A more detailed analysis of this issue shows that aversive stimuli do not necessarily activate dopamine transmission. While dopamine in the prefrontal cortex and in the nucleus accumbens core are monophasically increased by aversive stimuli, the response of dopamine transmission in the nucleus accumbens shell is more complex, with a decrease during the action of the aversive stimulus followed by an increase after its termination. This is the case of forced swim, tail-pinch and aversive tastes (Tanda et al., 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).

11. An operational framework for analyzing the role of dopamine in motivation

In principle, dopamine might be involved in any of the following aspects of motivation:

(1) hedonic impact of rewards; (2) stimulus–reward association; (3) explicit attribution of motivational value to the stimulus (incentive learning of Dickinson); (4) incentive activation/incentive salience attribution (Berridge, 1996); (5) complex sensory-motor integration (Salamone, 1992).

Experimentally, it is possible to distinguish an acquisition phase made up of steps (1) and (2) from an expression phase made up of steps (3), (4) and (5) by performing reward reinforcement in one trial and test its efficiency on a separate trial. This allows testing for the effect of drugs that interfere with dopamine transmission on acquisition as separate from expression of motivation.

Results of such studies performed with place and taste conditioning paradigms, operant responding and reinforced running in a straight runway are all consistent with separate roles of dopamine in acquisition and expression of motivation (see Sections 7–9).

A release of dopamine in relation to acquisition rather than expression would suggest an active role of dopamine in learning. This is the case of dopamine in the shell of the nucleus accumbens which does not respond to secondary stimuli but to primary stimuli and only when learning has still to take place; in the case of the prefrontal cortex and of the nucleus accumbens core, the responsiveness of dopamine transmission to the primary stimulus is not abolished by learning and a response to secondary stimuli is acquired (Bassareo and Di Chiara, 1997, 1999). A role of dopamine in acquisition explains the extinction-like effects of neuroleptics on primary reinforcement as related to an action on stimulus-reward learning while a role of dopamine in expression explains the effect of neuroleptics on locomotion, secondary reinforcement and incentive responding as related to either an incentive role (Berridge and Robinson, 1998) or to a complex sensory-motor role (Salamone, 1992) or both. While nucleus accumbens shell dopamine would play a role in acquisition (primary reinforcement), dopamine of the nucleus accumbens core and prefrontal cortex would be involved in expression (incentive and secondary responding).

12. Addictive drugs as false homologues (surrogates) of conventional reinforcers

A comparison between drug and non-drug reinforcers is justified by their behavioural and neurochemical similarities. Thus, drug and non-drug reinforcers 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 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 central neurochemical effects of conventional reinforcers that are the substrate of their motivational effects (Di Chiara et al., 1993a,b).

Addictive drugs, however, differ from conventional reinforcers 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 short-term habituation (Pettit and Justice, 1989, 1991; Wise et al., 1995a,b; Hemby et al., 1997). 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 the constraint of 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 capable of controlling behaviour in the exclusive and dominant manner typical of addiction.

Another differential aspect of drug reward as compared to conventional reward regards the lack of drug-induced satiation. Tolerance cannot be equated to satiety since it takes place only after a long-term exposure to the drug in contrast to satiety that is a short-term adaptive mechanism. As a result of lack of satiation the rewarding effect of the drug is maintained in spite of its repeated availability.

The property of drugs that allows these adaptive differences with conventional reinforcers is a basic one: drugs do not depend as conventional reinforcers from stimulation of peripheral sensory receptors for the induction of their motivational effects; drugs enter the brain and directly activate the critical central mechanism that is indirectly activated by conventional reinforcers. As a result of this short-circuit mechanism, drugs escape adaptive modulation which instead constrains the action of conventional reinforcers.

13. Tolerance and dependence of dopamine transmission

Abstinence from chronic exposure to addictive drugs of different classes has been reported to induce a state of ''anhedonia'' and dysforia that is expressed by a reduction of the reinforcing properties of natural rewards and electrical brain stimulation (see Di Chiara, 1995 for review; Koob et al., 1997). Associated to this aversive state is a reduction of in vivo dopamine transmission in the nucleus accumbens and in the activity of dopamine units in the ventral tegmentum. These changes have been observed following abstinence from morphine, amphetamine, ethanol and Δ^9 THC and appear dissociated from the physical signs of abstinence (Acquas and Di Chiara, 1992; Acquas et al., 1991; Pothos et al., 1991; Rossetti et al., 1992; Diana et al., 1993, 1995). Therefore, reduction of dopamine transmission in the nucleus accumbens, like impairment of self-stimulation, appears a more sensitive, longer lasting and more general sign of dependence than physical signs of abstinence.

Reduction of dopamine transmission in the nucleus accumbens following chronic drug exposure can be readily interpreted as the result of adaptive turning off of endogenous excitatory input on dopamine neurons secondary to the chronic drug-induced stimulation of dopamine transmission. However, it might also be the result of the unavoidable aversive state induced by abstinence. According to the first interpretation, reduction of dopamine release in the nucleus accumbens would contribute to the negative state of abstinence while in the second case would be a consequence of it. Consistent with the second possibility is the fact that the aversive state of abstinence generalizes to a pentylenetetrazol stimulus (Emmett-Oglesby et al., 1990). In the prefrontal cortex, abstinence is associated to an increase of dopamine release (Bassareo et al., 1995). It is notable that a pattern of increased dopamine release in the prefrontal cortex and a reduction in the nucleus accumbens shell is also observed following exposure to a mild aversive stimulus like tail-pinch or to a strong one like forced swim. These observations are consistent with the possibility that also the changes in dopamine transmission in the nucleus accumbens, and in the prefrontal cortex, are secondary to the unescapable aversive state of abstinence.

14. Sensitization

Repeated drug exposure has been reported to induce sensitization of drug-induced pre-synaptic stimulation of dopamine transmission in the ventral and in the dorsal striatum (see Di Chiara, 1995, for review). Existing studies, however, have not distinguished among nucleus accumbens shell and core; we have investigated by brain microdialysis the responsiveness of dopamine transmission in the nucleus accumbens shell and core in rats behaviourally sensitized by three different drugs: morphine, amphetamine and cocaine. In all three instances no sensitization of dopamine responsiveness to drug challenge was observed in the nucleus accumbens shell; in the case of morphine a significant reduction of the dopamine response was obtained. On the other hand in the nucleus accumbens core, sensitization of dopamine responsiveness to drug challenge was observed with morphine at 1.0 and 5.0 mg/kg s.c. and with amphetamine at 0.25 and 0.5 mg/kg s.c. but not with cocaine at any of the doses tested (5.0 and 10.0 mg/kg i.p.) (Cadoni and Di Chiara, 1999).

These results indicate that behavioural sensitization is not associated to changes in drug-induced stimulation of presynaptic dopamine transmission in the nucleus accumbens shell. As to the nucleus accumbens core, there seems

to be no consistent relationship among different drugs even of the same class (e.g., cocaine and amphetamine) between pre-synaptic sensitization of dopamine transmission and behavioral sensitization; this conclusion is in agreement with the results of various studies which failed to show a relationship between behavioral and pre-synaptic sensitization of dopamine responsiveness in the Nucleus accumbens (see Di Chiara, 1995, for review). On the other hands, intermittent morphine administration increases the expression of pre-prodynorphin particularly in dorso-lateral aspects of the striatum which are likely to be involved in motor behavior (Tjon et al., 1997). These observations suggest that post-synaptic rather than pre-synaptic changes play a major role in behavioural sensitization. The observation that these changes take place in the dorsal striatum (dorsal caudate–putamen) rather than in the nucleus accumbens, is consistent with the motor nature of behavioural sensitization.

Robinson and Berridge (1993), mainly on the basis of studies on psychostimulants, have proposed an incentive sensitization theory of drug addiction. This hypothesis posits that repeated drug exposure induces a state of sensitization of dopamine neurons; as a result of this, adaptive change stimuli that activate the dopamine system such as drug-related stimuli become more effective in stimulating dopamine transmission in mesocorticolimbic areas. According to this hypothesis, craving would be an incentive state (wanting) resulting from the release of dopamine by drug-related cues in the mesocorticolimbic areas. However, if dopamine neurons are sensitized they should respond in a sensitized fashion not only to drug-related incentives but also to drug-unrelated incentives. Therefore, this hypothesis apparently predicts that craving should develop not only to drug-related but also to drug-unrelated incentives a prediction in contrast with the strong stimulus-specificity of addictive behaviour (O'Brien et al., 1992).

According to the incentive-sensitization theory, drug-conditional stimuli and drug cues release dopamine or potentiate drug-induced stimulation of dopamine transmission in the nucleus accumbens (Robinson and Berridge, 1993). Contrary to this prediction, however, operant presentation of a light cue predictive of cocaine i.v. infusion failed to release dopamine in the nucleus accumbens from the first extinction test (Neisewander et al., 1996). Moreover, a single non-contingent i.v. 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). Therefore, in contrast with the incentive-sensitization theory, drug-conditioned stimuli as well as drug cues do not stimulate nor potentiate in vivo dopamine transmission in the nucleus accumbens. Recently, a 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 different technique (Di Ciano et al., 1998b).

An individual sensitization of dopamine responsiveness to drugs (not to drug-related incentives as in the hypothesis of Robinson and Berridge (1993) has been proposed as a factor that increases the vulnerability to initiation of drug use (Piazza and Le Moal, 1996; Piazza et al., 1989, 1990). This hypothesis is not incompatible with the stimulus requirements of drug addiction. In fact, due to the non-associative nature of sensitization, any drug would be a good candidate for self-administration in sensitized subjects. In these subjects, a sensitized response of dopamine transmissions to the drug would facilitate the abnormal learning process thus making them more vulnerable to drug addiction.

15. Stages of drug self-administration

We view drug addiction as the result of the action of various factors: (1) the rewarding properties of drugs; (2) their ability of activating dopamine transmission in the nucleus accumbens shell; (3) the individual sensitivity of dopamine transmission to the drug; (4) the resistance of the above properties to adaptive modulation (satiation, habituation) after repeated drug exposure; (5) the adaptive changes induced by repeated drug exposure resulting in the negative emotional state of abstinence. As the action of these factors is time dependent, drug addiction undergoes different phases or stages.

In the stage of *controlled drug use*, as a result of curiosity, peer pressure, social factors, personality traits etc., the subject comes into contact with a drug with addictive liability. The reinforcing properties of the drug (1st factor) facilitate further exposure to the drug while its associative learning properties related to release of dopamine in the nucleus accumbens shell (2nd factor) eventually amplified by individual sensitivity of dopamine transmission to the drug (3rd factor) promote the acquisition of incentive stimuli predictive of drug availability. In this stage the subject responds to the drug and to drug-related stimuli in a controlled manner not dissimilar from normal motivated responding.

With repeated drug exposure the subject progressively enters the stage of *drug abuse*. In this stage the repeated association of drug reward and drug-related stimuli in the presence of a non-habituating stimulation of dopamine transmission in the nucleus accumbens shell (4th factor) results in the attribution of excessive motivational value to drug-associated stimuli. In this stage the subject can still control drug intake in the absence of drug-related stimuli. Their presence, however, elicits compulsive drug-seeking eventually associated to drug urges (craving).

The stage of *addiction* is characterized by the condition of the preceding stage to which is added that of tolerance and dependence. In this stage, abstinence results in a negative emotional state (5th factor) which maintains the motivational relationship between the subject and the drug in the intervals when drug-conditioned incentives are not available. Moreover, the need state of abstinence amplifies the incentive properties of drug-related stimuli. It should be noted here that, even in presence of the negative motivational state of abstinence, the drug remains the positive reinforcer which maintains responding in spite of the fact that the hedonic properties of the drug (rush) have been reduced by tolerance. This condition, might constitute the basis for the escalating dose/binge pattern of drug-taking behavior typical of psychostimulant addiction.

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References

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

Acquas, E., Di Chiara, G., 1992. Depression of mesolimbic dopamine transmission and sensitization to morphine during opiate abstinence. J. Neurochem. 58, 1620–1625.

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.

Acquas, E., Carboni, E., Leone, P., Di Chiara, G., 1989. SCH 23390 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., Carboni, E., Di Chiara, G., 1991. Profound depression of mesolimbic dopamine release after morphine withdrawal in dependent rats. Eur. J. Pharmacol. 193, 133–134.

Alheid, G.F., Heimer, L., 1988. New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid and corticopetal components of substantia innominata. Neuroscience 27, 1–39.

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

Barrot, M., Marinelli, M., Abrous, D.N., Rougé-Pont, F., Le Moal, M., Piazza, P.V., 1998. Functional heterogeneity in dopamine release and in the expression of Fos-like proteins within the rat striatal complex. Eur. J. Neurosci., in press.

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., Di Chiara, G., 1995. Increase of extracellular dopamine in the medial prefrontal cortex during spontaneous and naloxone-precipitated opiate abstinence. Psychopharmacology 122, 202–205.

Bassareo, V., Tanda, G., Petromille, 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.

Bell, J., Bowron, P., Lewis, J., Batey, R., 1990. Serum levels of methadone in maintenance clients who persist in illicit drug use. Br. J. Addict. 85, 1599–1602.

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

Beninger, R.J., Phillips, A.G., 1980. The effect of pimozide on the establishment of conditioned reinforcement. Psychopharmacology 68, 147–153.

Beninger, R.J., Phillips, A.G., 1981. The effects of pimozide during pairing on the transfer of classical conditioning to an operant discrimination. Pharmacol. Biochem. Behav. 14, 101–105.

Beninger, R.J., Mason, S.T., Phillips, A.G., Fibiger, H.C., 1980. The use of extinction to investigate the nature of neuroleptic-induced avoidance deficits. Psychopharmacology 69, 11–18.

Berridge, K.C., 1996. Food reward: brain substrates of wanting and liking. Neurosci. Biobehav. Rev. 20, 1–25.

Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience?. Brain Res. Rev. 28, 309–369.

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

Bindra, D., 1978. How adaptive behavior is produced: a perceptual-motivation alternative to response reinforcement. Behav. Brain Sci. 1, 41–91.

Blackburn, J.R., Phillips, A.G., Fibiger, H.C., 1987. Dopamine and preparatory behavior: I. Effects of pimozide. Behav. Neurosci. 101, 352–360.

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

Brauer, L.H., De Wit, H., 1996. Subjective responses to D-amphetamine alone and after pimozide pretreatment in normal, healthy volunteers. Biol. Psychiatry 39, 26–32.

Brauer, L.H., De Wit, H., 1997. High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. Pharmacol. Biochem. Behav. 56, 265–272.

Brauer, L.H., Goooudie, A.J., de Wit, H., 1997. Dopamine ligands and the stimulus effects of amphetamine: animal models versus human laboratory data. Psychopharmacology 130, 2–13.

Brazell, M.P., Mitchell, S.N., Joseph, M.H., Gray, J.A., 1990. Acute administration of nicotine increases the in vivo extracellular levels of dopamine, 3,4-dihydroxyphenylacetic acid and ascorbic acid preferentially in the nucleus accumbens of the rat: comparison with caudate–putamen. Neuropharmacology 29, 1177–1185.

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.

Carboni, E., Imperato, A., Perezzani, L., Di Chiara, G., 1989. Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. Neuroscience 28, 653–661.

Cass, W.A., Gerhardt, G.A., Mayfield, R.D., Curella, P., Zahniser, N.R., 1992. Differences in dopamine clearance and diffusion in rat striatum and nucleus accumbens following systemic cocaine administration. J. Neurochem. 59, 259–266.

Caulliez, R., Meile, M.-J., Nicolaidis, S., 1996. A lateral hypothalamic

D1 dopaminergic mechanism in conditioned taste aversion. Brain Res. 729, 234–245.
Childress, A.R., McLellan, A.T., Ehrman, R., O'Brien, C.P., 1988. Classically conditioned responses in opioid and cocaine dependence: a role in relapse? In: Learning Factors in Substance Abuse. NIDA Research Monograph 94, Washington, DC, US Government Print Office, pp. 25–43.
De Vos, J.W., van Wilgenburg, H., van den Brink, W., Kaplan, C.D., de Vries, M.W., 1996. Patterns of craving and pharmacokinetics in long-term opiate addicts in methadone maintenance. Addict Res., in press.
Diana, M., Pistis, M., Carboni, S., Gessa, G.L., Rossetti, Z.L., 1993. Profound decrement of mesolimbic dopaminergic neuronal activity during ethanol withdrawal syndrome in rats: electrophysiological and biochemical evidence. Proc. Natl. Acad. Sci. U.S.A. 90, 7966–7969.
Diana, M., Pistis, M., Muntoni, A., Gessa, G.L., 1995. Profound decrease of mesolimbic dopaminergic neuronal activity in morphine withdrawn rats. J. Pharmacol. Exp. Ther. 272, 781–785.
Di Chiara, G., 1991. On the preferential release of mesolimbic dopamine by amphetamine. Neuropsychopharmacology 5, 243–244.
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 dopamine in compulsive drug use. J. Psychopharmacol. 12, 54–67.
Di Chiara, G., Imperato, A., 1988a. 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., Imperato, A., 1988b. Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J. Pharmacol. Exp. Ther. 244, 1067–1080.
Di Chiara, G., Acquas, E., Tanda, G., Cadoni, C., 1993a. Drugs of abuse: biochemical surrogates of specific aspects of natural reward?. Biochem. Soc. Symp. 59, 65–81.
Di Chiara, G., Tanda, G., Frau, R., Carboni, E., 1993b. On the preferential release of dopamine in the nucleus accumbens by amphetamine: further evidence obtained by vertically implanted concentric dialysis probes. Psychopharmacology 112, 398–402.
Di Ciano, P., Blaha, C.D., Phillips, A.G., 1998a. 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.
Di Ciano, P., Blaha, C.D., Phillips, A.G., 1998b. The relation between dopamine oxidation currents in the nucleus accumbens and conditioned increases in motor activity in rats following repeated administration of D-amphetamine or cocaine. Eur. J. Neurosci. 10, 1113–1120.
Dickinson, A., Balleine, B., 1995. Motivational control of instrumental action. Curr. Dir. Psychol. Sci. 4, 162–167.
Emmett-Oglesby, M.W., Mathis, D.A., Moon, R.T.Y., Lal, H., 1990. Animal models of drug withdrawal symptoms. Psychopharmacology 101, 292–309.
Ettenberg, A., 1989. Dopamine, neuroleptics and reinforced behavior. Neurosci. Biobehav. Rev. 13, 105–111.
Ettenberg, A., 1990. Haloperidol prevents the reinstatement of amphetamine-rewarded runway responding in rats. Pharmacol. Biochem. Behav. 36, 635–638.
Ettenberg, A., Horvitz, J.C., 1990. Pimozide prevents the response-reinstating effects of water reinforcement in rats. Pharmacol. Biochem. Behav. 37, 465–469.
Ettenberg, A., MacConell, L.A., Geist, T.D., 1996. Effects of haloperidol in a response-reinstatement model of heroin relapse. Psychopharmacology 124, 205–210.
Fischman, M.W., 1989. Relationship between self-reported drug effects and their reinforcing effects: studies with stimulant drugs. NIDA Res. Monogr. 92, 211–230.
Franklin, K.B.J., 1978. Catecholamines and self-stimulation: reward and performance deficits dissociated. Pharmacol. Biochem. Behav. 9, 813–820.
Franklin, K.B.J., McCoy, S.N., 1979. Pimozide-induced extinction in rats: stimulus control of responding rules out motor deficit. Pharmacol. Biochem. Behav. 11, 71–76.
Gallistel, C.R., Boytim, M., Gomita, Y., Kebanoff, L., 1982. Does pimozide block the reinforcing effect of brain stimulation?. Pharmacol. Biochem. Behav. 17, 769–781.
Gessa, G.L., Muntoni, F., Collu, M., Vargiu, L., Mereu, G.P., 1985. Low doses of ethanol activate dopaminergic neurons in the ventral tegmental area. Brain Res. 348, 201–203.
Goldberg, S.R., 1976. Stimuli associated with drug injections as events that control behavior. Pharmacol. Rev. 27, 325–340.
Gratton, A., Wise, R.A., 1994. Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats. J. Neurosci. 14, 4130–4146.
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 [letter]. Science 278, 1548–1549.
Grill, H.J., Norgren, R., 1978. The taste reactivity test: I. Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res. 143, 263–279.
Heidbreder, C., Feldon, J., 1998. Amphetamine-induced neurochemical and locomotor responses are expressed differentially across the anteroposterior axis of the core and shell subterritories of the nucleus accumbens. Synapse 29, 310–322.
Heimer, L., Wilson, R.D., 1975. The subcortical projections of allocortex: similarities in the neuronal associations of the hippocampus, the piriform cortex and the neocortex. In: Santini, M. (Ed.), Golgi Centennial Symposium Proceedings. Raven Press, New York, pp. 173–193.
Heimer, L., de Olmos, J., Alheid, G.F., Zaborszky, L., 1991. 'Perestroika' in the basal forebrain: opening the border between neurology and psychiatry. Prog. Brain Res. 87, 109–165.
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.
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.
Hill, R.T., 1970. Facilitation of conditioned reinforcement as a mechanism of psychomotor stimulation. In: Costa, E., Garattini, S. (Eds.), Amphetamine and Related Compounds. Raven Press, New York.
Himmelsbach, C.K., 1943. Morphine, with reference to physical dependence. Fed. Proc. 2, 201–203.
Hitchcott, P.K., Phillips, G.D., 1998. Double dissociation of the behavioural effects of R(+) 7-OH-DPAT infusions in the central and basolateral amygdala nuclei upon Pavlovian and instrumental conditioned appetitive behaviours. Psychopharmacology 140, 458–469.
Hitchcott, P.K., Bonardi, C.M.T., Phillips, G.D., 1997a. Enhanced stimulus-reward learning by intra-amygdala administration of a D-3 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.
Holland, P.C., Straub, J.J., 1979. Differential effects of two ways of devaluing the unconditioned stimulus after Pavlovian appetitive conditioning. J. Exp. Psychol. Anim. Behav. 5, 65–78.
Horns, W.H., Rado, M., Goldstein, A., 1975. Plasma levels and symptom complaints in patients maintained on daily dosage of methadone hydrochloride. Clin. Pharm. Ther. 17, 636–649.
Horvitz, J.C., Ettenberg, A., 1988. Haloperidol blocks the response reinstating effects of food reward: a methodology for separating

neuroleptic effects on reinforcement and motor processes. Pharmacol. Biochem. Behav. 31, 861–865.
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.
Imperato, A., Di Chiara, G., 1986. Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. J. Pharmacol. Exp. Ther. 239, 219–228.
Imperato, A., Mulas, A., Di Chiara, G., 1986. Nicotine preferentially stimulates dopamine released in the limbic system of freely moving rats. Eur. J. Pharmacol. 132, 337–338.
Johanson, C.E., 1978. Drugs as reinforcers. In: Blackman, D.E., Sanger, D.J. (Eds.), Contemporary Research in Behavioral Pharmacology. Plenum, New York, pp. 325–390.
Kiyatkin, E.A., Gratton, A., 1994. Electrochemical monitoring of extracellular dopamine in nucleus accumbens of rats lever-pressing for food. Brain Res. 652, 225–234.
Kiyatkin, E.A., Stein, E.A., 1996. Fluctuations in nucleus accumbens dopamine during cocaine self-administration behavior: an in vivo electrochemical study. Neuroscience 64, 599–614.
Kiyatkin, E.A., Wise, R.A., Gratton, A., 1993. Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous heroin self-administration in rats. Synapse 14, 60–72.
Konorski, J., 1967. Integrative activity of the brain. Univ. of Chicago Press.
Koob, G.F., Caine, S.B., Parsons, L., Markou, A., Weiss, F., 1997. Opponent process model and psychostimulant addiction. Pharmacol. Bioochem. Behav. 57, 513–521.
Koob, G.F., Stinus, L., Le Moal, M., Bloom, F.E., 1989. Opponent process theory of motivation: neurobiological evidence from studies of opiate dependence. Neurosci. Biobehav. Rev. 13, 135–140.
Kuczenski, R., Segal, D.S., 1992. Differential effects of amphetamine and dopamine uptake blockers (cocaine, nomifensine) on caudate and accumbens dialysate dopamine and 3-methoxytyramine. J. Pharmacol. Exp. Ther. 262, 1085–1094.
Le Magnen, J., 1969. Peripheral and systemic actions of food in the caloric regulation of intake. Ann. NY Acad. Sci. 157, 1126–1157.
Loimer, N., Schmid, R., 1992. The use of plasma levels to optimize methadone maintenance treatment. Drug Alcohol Depend. 30, 241–246.
Mackintosh, N.J., 1974. The Psychology of Animal Learning. Academic Press, London.
Mark, G.P., Blander, D.S., Hoebel, B.G., 1991. A conditioned stimulus decreases extracellular dopamine in the nucleus accumbens after the development of a learned taste aversion. Brain Res. 551, 308–310.
Markou, A., Koob, G.F., 1991. Postcocaine anhedonia. An animal model of cocaine withdrawal. Neuropsychopharmacology 4, 17–26.
McFarland, K., Ettenberg, A., 1995. Haloperidol differentially affects reinforcement and motivational processes in rats running an alley for intravenous heroin. Psychopharmacology 122, 346–350.
McFarland, K., Ettenberg, A., 1997. Reinstatement of drug-seeking behavior produced by heroin-predictive environmental stimuli. Psychopharmacology 131, 86–92.
Matthews, R.T., German, D.C., 1984. Electrophysiological evidence for excitation of rat ventral tegmental area dopamine neurons by morphine. Neuroscience 11, 617–628.
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.
Mogenson, G.J., Jones, D.L., Yim, C.Y., 1980. From motivation to action: functional interface between the limbic system and the motor system. Prog. Neurobiol. 14, 69–97.
Neisewander, J.L., O'Dell, L.E., Ly, M.A., Tran-Nguyen, T.L., Castañeda, M.A.E., Fuchs, R.A., 1996. Dopamine overflow in the nucleus accumbens during extinction and reinstatement of cocaine. Neuropsychopharmacology 15, 506–514.
O'Brien, C.P., Childress, A.R., McLellan, A.T., Ehrman, R., 1992. Classical conditioning in drug-dependent humans. In: The Neurobiology of Drug and Alcohol Addiction. Ann. NY Acad. Sci. 654, 400–415.
Orzi, F., Passarelli, F., La Riccia, M., Di Grezia, R., Pontieri, F.E., 1996. Intravenous morphine increases glucose utilization in the shell of the rat nucleus accumbens. Eur. J. Pharmacol. 302, 49–51.
Palkovits, M., 1979. Dopamine Levels of Individual Brain Regions: Biochemical Aspects of dopamine Distribution in the Central Nervous System. Academic Press, London, pp. 343–356.
Pavlov, I.P., 1927. Conditioned Reflexes. Oxford Univ. Press, London, p. 12.
Peciña, S., Berridge, K.C., Parker, L.A., 1997. Pimozide does not shift palatability: separation of anhedonia from sensorimotor effects. Pharmacol. Biochem. Behav. 58, 801–811.
Pettit, 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.
Pettit, 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.
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.
Piazza, P.V., Le Moal, M., 1996. Pathophysiological basis of vulnerability to drug abuse: Role of an interaction between stress, glucocorticoids, and dopaminergic neurons. Annu. Rev. Pharmacol. Toxicol. 36, 359–378.
Piazza, P.V., Deminière, J.M., Le Moal, M., Simon, H., 1989. Factors that predict individual vulnerability to amphetamine self-administration. Science 245, 1511–1513.
Piazza, P.V., Deminière, J.-M., Le Moal, M., Simon, H., 1990. Stress- and pharmacologically induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. Brain Res. 514, 22–26.
Pontieri, F.E., Colangelo, V., La Riccia, M., Pozzilli, C., Passarelli, F., Orzi, F., 1994. Psychostimulant drugs increase glucose utilization in the shell of the rat nucleus accumbens. NeuroReport 5, 2561–2564.
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 similarity to those of addictive drugs. Nature 382, 255–257.
Pothos, E., Rada, P., Mark, G.P., Hoebel, B.G., 1991. Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. Brain Res. 566, 348–350.
Radhakishun, F.S., Van Ree, J.M., Westearink, H.B.C., 1988. Scheduled eating increases dopamine release in the nucleus accumbens of food-deprived rats as assessed with on-line brain microdialysis. 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.
Redgrave, P., Prescott, T.J., Gurney, K., 1999. Is the short-latency dopamine response too short to signal reward error?. TINS 22, 146–151.
Rescorla, R.A., Solomon, R.L., 1967. Two-process learning theory: relationship between Pavlovian conditioning and instrumental learning. Psychol. Rev. 74, 151–182.
Richardson, N.R., Gratton, A., 1996. Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. J. Neurosci. 16, 8160–8169.

Robbins, T.W., 1975. The potentiation of conditioned reinforcement by psychomotor stimulant drugs: a test of Hill hypothesis. Psychopharmacol. 45, 103–114.

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.

Robinson, T.E., Camp, D.M., 1990. Does amphetamine preferentially increase the extracellular concentration of dopamine in the mesolimbic system of freely moving rats?. Neuropsychopharmacology 3, 163–173.

Rossetti, Z.L., Hmaidan, Y., Gessa, G.L., 1992. Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. Eur. J. Pharmacol. 221, 227–234.

Salamone, J.D., 1992. Complex motor and sensorimotor functions 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.

Salamone, J.D., Cousins, M.S., Snyder, B.J., 1997. Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. Neurosci. Biobehav. Rev. 21, 341–359.

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

Schneirla, T.C., 1959. An evolutionary and developmental theory of biphasic processes underlying approach and withdrawal. In: Jones, M.R. (Ed.), Nebraska Symposium on Motivation. Univ. of Nebraska Press, Lincoln, pp. 1–42.

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.

Skinner, B.F., 1935. Two types of conditioned reflex and a pseudotype. J. Gen. Psychol. 12, 66–77.

Skinner, B.F., 1937. Two types of conditioned reflex: a reply to Konorski and Miller. J. Gen. Psychol. 16, 272–279.

Solomon, R.L., 1977. An opponent-process theory of motivation: IV. The affective dynamics of addiction. In: Maser, J.D., Seligman, M.E.P. (Eds.), Psychopathology: Experimental Models. Freeman, San Francisco.

Stewart, J., de Wit, H., Eikelboom, R., 1984. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychol. Rev. 91, 251–268.

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., 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., 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 blockade of the noradrenaline carrier to the increase of extracellular dopamine in the rat prefrontal cortex by amphetamine and cocaine. Eur. J. Neurosci. 9, 2077–2085.

Tjon, G.H.K., Voorn, P., Vanderschuren, L.J.M.J., De Vries, T.J., Michiels, N.H.L.M., Jonker, A.J., Klop, H., Nestby, P., Mulder, A.H., Schoffelmeer, A.N.M., 1997. Delayed occurrence of enhanced striatal preprodynorphin gene expression in behaviorally sensitized rats: differential long-term effects of intermittent and chronic morphine administration. Neuroscience 76, 167–176.

Westerink, B.H.C., 1995. Brain microdialysis and its application for the study of animal behavior. Behav. Brain Res. 70, 103–124.

Wikler, A., 1973. Dynamics of drug dependence: implications of a conditioning theory for research and treatment. Arch. Gen. Psychiatry 28, 611–616.

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

Wise, R.A., 1985. The anhedonia hypothesis: Mark III. Behav. Brain Sci. 8, 178–186.

Wise, R.A., Bozarth, M.A., 1987. A psychomotor stimulant theory of addiction. Psychol. Rev. 94, 469–492.

Wise, R.A., Leone, P., Rivest, P., Leeb, K., 1995a. Elevations of nucleus accumbens 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.

Young, A.M.J., 1994. Intracerebral microdialysis in the study of physiology and behavior. Rev. Neurosci. 4, 373–395.

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.

Young, A.M.J., Ahier, R.G., Upton, R.L., Joseph, M.H., Gray, J.A., 1998. Increased extracellular dopamine in the nucleus accumbens of the rat during associative learning of neutral stimuli. Neuroscience 83, 1175–1183.