hydrate moieties have been related functionally to dopamine transport, but not to the binding of cocaine and analogues to dopamine transporters [9,10]. The protein has consensus phosphorylation sites although it is not yet known if phosphorylation plays a role in regulating the activity of the transporter [11]. A major development has been the cloning of the cDNA for the dopamine transporter in the rat [12–14], cow [15] and human [16,17]. Of particular interest is the finding that dopamine transport can be conferred on a cell by transfecting with the single cloned cDNA, suggesting that the dopamine transporter is composed of a single protein that may or may not function as a multimeric unit [12,18]. Since binding studies have suggested for a long time that cocaine and dopamine interact competitively and that there is likely to be some overlap in their binding sites, it appears that cocaine binding sites are located on the single transporter protein and not on a different subunit of a multimeric complex or on another interacting protein.

With the knowledge that cocaine binding sites on dopamine transporters appear to be associated with the initiation of its reinforcing or addicting effects, there have been significant efforts to find a cocaine antagonist at this site which would serve as an effective pharmacological intervention in the prevention and treatment of cocaine abuse. Such a compound would presumably interfere with cocaine binding, yet spare the process of dopamine uptake so that extracellular levels of dopamine would not be increased [19]. Unfortunately, such a compound has not been found to date. Many compounds, however, have been shown to produce the opposite effect, potently inhibiting dopamine transport without affecting cocaine binding to the same degree. Recent studies utilizing site-directed mutagenesis indicate that the binding of cocaine to the transporter can be altered independently of functional changes in dopamine uptake [20]. Thus, although it is not yet clear whether it will be possible to develop a useful cocaine antagonist, mutagenesis studies indicate a possible functional separation between dopamine transport and cocaine binding. The current rapid advances in molecular studies will increase our understanding of cocaine's interaction with neuronal transporters [11–13].

Recent studies have shown that administration of cocaine and amphetamine can cause changes in oncogene expression in dopamine nerve terminal regions [21,22]. Expression of these genes indicates that the action of psychostimulants may lead to other significant changes in gene expression and substantial biochemical changes in post-synaptic neurons. Chronic cocaine administration also produces changes in dopamine transport [23]. While there are conflicting results in the literature, it appears that conditions, doses and total quantities of drug vary among the different investigators. In any case, it is clear that cocaine exerts a powerful effect on neuronal circuits containing dopamine neurons such that the expression and function of neuronal proteins may be altered [24].

Biochemical studies have also provided evidence which is consistent with the hypothesis that dopaminergic neurotransmission is fundamental to the reinforcing properties of many drugs of abuse, not just cocaine. In particular, brain dialysis, a procedure in which a small probe is implanted into the brain in order to measure local extracellular dopamine levels, has shown that many drugs which are abused by humans preferentially increase dopamine efflux in limbic areas of the brain, especially in the nucleus accumbens, while drugs which are not abused do not have this effect (see Di Chiara *et al.*, this volume). In particular, opiates, nicotine, amphetamine, and cocaine

have been shown to increase extracellular concentrations of dopamine in the nucleus accumbens [25]. Interestingly, other drugs tested with aversive properties (e.g. agonists of κ-opioid receptors, U-50,488, tifluadom, and bremazocine) reduced dopamine release in the accumbens and in the caudate. Drugs not abused by humans such as imipramine, atropine and diphenhydramine did not alter dopamine concentrations. There are some discrepancies in published reports of research using slightly different experimental arrangements. Nevertheless, the results of several studies are completely consistent with the well-known effects of cocaine as a blocker of dopamine uptake [26–30]. Thus, if there are disagreements regarding this issue, they are not concerned with whether or not cocaine and amphetamine cause extracellular dopamine build-up in mesolimbic regions, but rather with the precise role of these neurons in reinforcement, and the significance of the changes.

Behavioural studies

Studies of the structure–activity requirements for cocaine binding at the dopamine transporter have yielded highly potent cocaine analogues which are more potent with respect to both binding at the dopamine transporter and activity in behavioural assays [31–33]. Some of these compounds have been utilized as radiolabelled binding ligands in studies of the relationship between receptor occupancy and changes in locomotor activity. These studies suggest that a fairly high degree of occupancy (about 70%) is needed to produce a lesser fractional level of maximal locomotor activity (about 25%) [33]. These data suggest that in a pharmacological sense, there are extra receptors for cocaine and that the decreases in transporters that might occur during aging [34] may not have functional impact, at least in the early stages of transporter loss. Moreover, in receptor binding studies *in vivo*, it has been shown that potent cocaine analogues accumulate in brain regions enriched with dopaminergic nerve terminals [35,36], supporting the view that dopaminergic mechanisms are involved.

Behavioural studies have utilized lesion techniques and pharmacological manipulations to elucidate the neuronal mechanisms associated with the reinforcing effects of psychostimulants. Dopaminergic neuronal systems, especially brain mesolimbic pathways, have been associated with the reinforcing effects of both cocaine and amphetamine. The effects of brain lesions on cocaine self-administration have provided support for the view that mesolimbic dopaminergic neurons support psychostimulant self-administration [37–41]. Current studies of this type are aimed at understanding more details of the neuronal circuitry involved in these pathways [42].

Neuropharmacological research has shown that selective dopaminergic receptor blockade attenuates the reinforcing properties of both (−)cocaine and (+)amphetamine in animals [43–50]. Dopaminergic agonists, in contrast, substitute for intravenous self-administration of cocaine and *d*-amphetamine [48,51].

Based on such a preponderance of evidence, from both receptor binding studies and neuropharmacological studies, that dopaminergic neurotransmission has a primary role in mediating the reinforcing effects of psychostimulants, pharmacotherapeutic strategies involving the utilization of dopamine receptor blockers are currently being considered as a potential approach for the treatment of cocaine abuse. Indeed, recent

experiments utilizing operant methods have attempted to determine the specific dopaminergic receptor subtypes which may be involved in mediating the reinforcing effects of cocaine. To date, it remains unclear whether either D_1 or D_2 receptors specifically mediate these drug effects [52–57]. Currently, it remains possible that interactions either between neurons receiving inputs from each of these receptors or between second messenger systems initiated by each of these receptors in individual neurons may be critical. Indeed, several studies have illustrated apparent cooperation between D_1 and D_2 receptors in the nucleus accumbens, in particular with respect to the induction of adenylyl cyclase [58], and synergism at the cellular level which may be associated with particular dopamine-related behavioural phenomena [59]. Regardless of this debate, however, it may be likely that D_1 antagonists may be more useful as clinical pharmacotherapies for psychostimulant abuse due to the lesser extrapyramidal side effects associated with these compounds relative to those for D_2 receptor antagonists [60,61]. Woolverton and Johnson [24] have recently reviewed this topic as well.

Continued use of cocaine can cause both tolerance and sensitization [24]. These changes in behaviour suggest that the use of cocaine must cause some changes in brain biochemistry. Indeed, it has been shown by many investigators using animal models that chronic cocaine alters levels of dopamine receptors in striatum and accumbens [47,62]. We have noted that the findings of many such studies are not completely consistent with each other and may depend on genetic differences between animal subjects or on differences in the specific experimental conditions utilized [1] (see Figs. 5–8 in Marley *et al.*, this volume). Differences between studies with regard to the time course of receptor changes may also explain inconsistencies in findings.

Human studies

The ultimate challenge of the dopamine hypothesis will obviously be to establish its relevance and importance in human addiction. As we previously reported [1], there is some evidence supporting the dopamine hypothesis in human subjects. For example, positron emission tomography techniques have indicated a similarity between the time course of cocaine's occupancy of the binding site at the transporter and the time course of associated psychological effects [63]. Using these methods, it has also been shown that post-synaptic dopaminergic D_2 receptors in striatum appear significantly decreased in cocaine abusers who have been detoxified for less than 1 week but receptor numbers appear similar to normal control subjects in cocaine abusers who have been detoxified for 1 month [64]. In frontal lobes of the brain, however, decreases in D_2 receptors and in glucose metabolism are associated with chronic cocaine use, and these effects appear to persist for 3–4 months following detoxification [65,66].

In an effort to extend the findings from studies using animal models, research has been performed to assess the influence of dopamine receptor blockers on the subjective effects of cocaine in humans. In an open trial, the neuroleptic flupenthixol decanoate was reported to result in a decreased craving for the drug with an increase in the average retention time that the patient remained in treatment [67]. However, these results have yet to be demonstrated in a double-blind study. It has also been reported that euphoria induced by amphetamine appears to be sensitive to dopamine receptor blockers [68]. In contrast to these results, haloperidol was reported to have no effect on cocaine-induced

rush, and only a limited effect on some of the subjective effects associated with drug 'liking' [69]. In yet another study, patients given haloperidol or chlorpromazine did not report a blockade of drug-induced euphoria or increased abstinence, although an attenuation of psychotic symptoms was observed [70].

Based upon the idea that dopaminergic neurotransmission is altered in chronic cocaine users and is associated with craving and the cocaine abstinence syndrome, dopaminergic agonists or indirect agonists have also been studied for their therapeutic value in treating cocaine abuse [1]. Recent studies which have tested this approach evaluated the effectiveness of amantadine as an adjunct treatment for cocaine abuse [71–73]. These studies indicated that this pharmacological treatment was associated with decreased craving, decreased cocaine use and decreases in several indices of psychiatric adjustment, although these effects were not significantly greater than those observed for placebo treatment groups. Similar results have been reported for desipramine, an indirect monoaminergic agonist [72–74]. Finally, although the dopaminergic agonist bromocriptine has been shown to antagonize decreases in cerebral glucose metabolism associated with abstinence from chronic cocaine treatment in rats [75], the results of another recent study utilizing cocaine-abusing subjects has shown that this potential pharmacotherapy has no significant effect on either physiological or subjective effects of cocaine which may be predictive of its therapeutic benefit [76].

Overall then, the limited number of pharmacological studies of cocaine effects in humans have provided inconsistent results, and have neither confirmed nor disproved the hypothesis that effective pharmacotherapies for psychostimulant abuse will focus on interactions with dopaminergic neuronal systems. Nevertheless, there are currently five known dopamine receptors, some with relatively unique pharmacological profiles. It is also possible that there are undiscovered, yet functionally important, dopamine receptors for which pharmacological profiles have not yet been developed. Further, if the psychotimimetic effects of psychostimulants are due to interactions at one or more of these known or unknown receptor sites, it may be difficult to establish the role of dopaminergic systems in human drug addiction by studying single dopamine receptor agonists or antagonists. Certainly, research focusing on the development of analogues for agents known to bind selectively to dopaminergic receptors may address these issues and, ultimately, yield more effective treatment alternatives. Studies are either planned or underway in several centres which will attempt to study these issues in more detail.

Dopamine plus other factors?

We have discussed the preponderance of evidence that indicates that specific dopaminergic systems may mediate initial reinforcement that leads to acquisition as well as maintenance of chronic use and abuse of psychostimulants. Is it likely, however, that the action of cocaine at the dopamine transporter is the sole and only required factor for producing its reinforcing properties? An inspection of available data suggests that the answer may be 'no'. The obvious difficulty with this suggestion is that not all dopamine uptake blockers are abused by humans. Correlational studies which show relationships between dopamine transporter blockade and drug reinforcement have been more or less limited to cocaine, its analogues and some other structurally and functionally related compounds [5,6]. In choice studies with humans, some but not all dopamine uptake

blockers are selected for self-administration and appear at least moderately reinforcing [77]. Thus, additional factors may also influence the reinforcing properties of cocaine and related psychostimulants. A mechanism could be proposed whereby inhibition of dopamine uptake is 'permissive' and some additional action of cocaine is critical for the full reinforcing effect of the drug. It also seems possible that dopamine is involved in initial stages of addiction and that other mechanisms are associated with more chronic effects of the drugs.

It is also possible to propose that those drugs which block dopamine uptake but which are not abused lack some quality that has nothing to do with receptors, but rather with pharmacokinetics. It has often been said that those drugs which enter the brain rapidly have the greatest abuse liability and this has intuitive validity. In this regard, it has been shown that cocaine enters the brain and occupies binding sites more rapidly than other uptake blockers such as GBR 12909 and mazindol. Mazindol was the slowest to enter the brain and occupy transporters in one study [78]. It is interesting that while this drug serves as a moderate reinforcer in some animals [79,80], it is thought to have low abuse potential in humans [77]. Pharmacokinetic factors are thought to underlie the apparent higher abuse liability of crack compared with cocaine. Crack or smoked cocaine, as opposed to nasally or orally administered drugs, enters the brain very rapidly [81,82]. Thus, there may be properties of cocaine in addition to its specific transporter targets which are important in facilitating its reinforcing effects.

Another possibility is that those drugs which block dopamine uptake but which are not abused have some other property or effect in the brain which precludes their abuse. For example, we have previously discussed benztropine and some tricyclic drugs in terms of their anticholinergic effects and lethality that would occur at doses lower than those necessary for dopamine transporter blockade [1,2,5].

From another perspective, behavioural pharmacology studies have also provided important information concerning the role of serotonergic neuronal systems in mediating the reinforcing effects of cocaine and amphetamine. Indeed, cocaine is multifunctional in that it inhibits dopamine uptake, serotonin uptake and norepinephrine uptake at roughly similar concentrations [32]. The relative affinity of cocaine at each of these sites may be important in determining its summed effects on neurotransmission within reward pathways of the brain. We have previously shown that the affinities of amphetamine and related compounds at serotonin uptake sites are inversely associated with the reinforcing potencies of these compounds in operant tests [83]. These results suggest that the rewarding effects of these drugs may be attenuated by serotonergic neuronal mechanisms, and are consistent with research illustrating that lesions of serotonergic neurons, with the neurotoxin 5,7-dihydroxytryptamine, increase rates of responding for intravenous administrations of *d*-amphetamine under commonly used fixed-ratio operant schedules of reinforcement [84]. In contrast, pretreatments with the serotonin precursor L-tryptophan or with serotonin uptake blockers decrease amphetamine-reinforced self-injections under similar operant conditions [85–88]. Using both receptor binding methods and operant techniques, we have previously shown that dopaminergic, but not serotonergic, neurotransmission is associated with the reinforcing effects of cocaine under operant conditions utilizing short test sessions and requiring fixed numbers of responses (FR10) in order to obtain the drug [5,89], while the potent serotonin uptake inhibitor fluoxetine appears to attenuate rates of responding for amphetamine [89]. These data suggest that serotonergic neuronal systems may indeed

attenuate the reinforcing potencies of amphetamine, but perhaps not cocaine under these conditions. However, some evidence suggests that serotonergic systems may also influence the reinforcing effects of cocaine under quite different operant conditions, specifically those involving continuous access to the drug over extended periods of time and those requiring the completion of an increasingly greater number of operant responses prior to administration of cocaine [88,90,91]. These results suggest that under these conditions, some factors associated with serotonergic neurotransmission may influence cocaine self-administration. The nature of these influences is as yet unknown, although they may be related to issues of motivational states or efficacy of the drug. It is quite possible that serotonergic neurons influence the motivational factors necessary for animals to exhibit extremely high levels of responding for drugs under operant conditions requiring the completion of large sequences of lever presses, such as that seen under progressive ratio schedules. Taken together, these research findings indicate that the reinforcing effects of psychostimulants and other drugs of abuse may be mediated by multiple, distinct influences, including the intrinsic reinforcing properties of the drug, perhaps primarily mediated by dopaminergic neurotransmission, as well as motivational factors, which might be more significantly mediated by serotonergic neurotransmitter systems.

Future directions for the development of pharmacological treatments for psychostimulant abuse

The abundant literature describing the neuropharmacology of the reinforcing effects of psychostimulants, and the potential success of using medication in treating human drug abusers has led to attempts to develop new medications. Some of the possible strategies for medications development are as follows.

1. A cocaine substitute which could function in a manner analogous to methadone in opiate treatment clinics (see Terenius, this volume) could be useful but none has yet been identified. In a study with methylphenidate [92], the drug appeared to initially reduce craving for cocaine but later increased craving. This result is not encouraging (it may support the dopamine hypothesis, however), but other investigators are currently testing the substitution strategy in the hopes of developing a drug which addicts can utilize in the initial stages of treatment to arrest or control the factors that lead to rapid relapse. The development of a large number of cocaine analogues [32] and other compounds which block the dopamine transporter has fuelled speculation that a substitute might be found.

2. A direct competitive cocaine antagonist at the dopamine transporter could be useful, but none has yet been found. However, site-directed mutagenesis studies suggest that cocaine binding can be altered independently of dopamine uptake [20].

3. Indirect antagonists of cocaine's actions, i.e. a blocker at dopamine receptors, might be effectively utilized as pharmacotherapeutic agents in the treatment of cocaine or other psychostimulant abuse. However, only a limited number of drugs have been tested [52–57,67,69,70]. It seems that a wider variety of dopamine receptor blocking drugs, and new drugs which serve as antagonists at the more recently discovered receptors, should be tested.

4. Interest in the efficacy of serotonin uptake blockers as adjunct pharmacotherapeutic agents in addiction treatment programmes has been increasing. Several lines

of evidence already discussed above suggest that serotonergic neurotransmission may mediate factors related to the reinforcing effects of psychostimulant drugs, including drug efficacy and motivational state. These same motivational factors may influence or, perhaps be analogous to, human craving for drugs. If so, continued chronic abuse of a drug may require not only specific reinforcing effects of a drug *per se*, but also motivational factors contributed by the subject. In general, the evidence suggests that enhancement of serotonergic neurotransmission appears to decrease psychostimulant self-administration. Thus, it seems possible that although dopaminergic neuronal systems may mediate the reinforcing properties of psychostimulants *per se*, other neurotransmitter systems, especially serotonergic systems, may influence motivational factors. Thus, pharmacotherapies enhancing serotonergic neurotransmission may attenuate the immediate reinforcing effects of psychostimulants or, perhaps, the subsequent craving effects.

5. Other antidepressants have been studied for their potential clinical efficacy in treating psychostimulant abuse, especially cocaine addiction. However, the findings to date indicate that many of these agents must be utilized with some caution. Recent evidence suggests that serotonergic and dopaminergic neurotransmission appear to be associated with the toxicities induced by administration of high doses of cocaine in animal models [93]. In addition, this research has shown that monoamine uptake blockers such as fluoxetine, desipramine and bupropion increase the frequency with which seizures and lethal responses are observed following administration of high doses of cocaine. Further, it has also recently been shown that monoamine uptake inhibitors, including GBR 12909, fluoxetine and desipramine, enhance the discriminative stimulus effects of cocaine in rats, suggesting that the subjective effects of these drugs may be enhanced in humans [94]. Finally, Fischman *et al.* [95] have recently reported that the cardiovascular effects of desipramine appear to enhance the potential for toxicity when this antidepressant is administered in conjunction with cocaine, and a number of adverse side effects contribute to treatment non-compliance by cocaine abusers [96]. Taken together, it seems clear that antidepressant drugs should be used with caution in the treatment of cocaine abuse.

6. There is evidence that other neurotransmitter systems, with which cocaine does not interact directly, may also influence the reinforcing or addictive effects of cocaine. Perhaps drugs targeting these systems will be useful medications. For instance, there is evidence for the influence of benzodiazepine receptors on cocaine self-administration in both humans and animals. First, carbamazepine has been shown to decrease cocaine use in cocaine-dependent methadone maintenance patients [97], although its interactions with cocaine with respect to human cardiovascular function may ultimately limit its clinical usefulness [98]. Second, another series of experiments has indicated that the benzodiazepine receptor agonist, chlordiazepoxide, also decreases cocaine-reinforced responding in rats [99], and this effect may be due to specific interactions between benzodiazepine receptors with dopaminergic neurons [100,101]. Indeed, midazolam has been shown by *in vivo* microdialysis techniques to decrease extracellular concentrations of dopamine [102]. Chronic cocaine ingestion has also been associated with increased ligand binding to brain benzodiazepine receptors in a rat model and in human platelets [103,104]. If further research is consistent with these findings, benzodiazepine agonists may prove to be clinically effective in the treatment of cocaine abuse. There is growing evidence that opiate compounds may also be effective as adjunct pharmacotherapeutic agents for the treatment of cocaine addiction. Buprenorphine, a

mixed opiate agonist–antagonist, and naltrexone, an opiate antagonist, have been shown to selectively decrease responding for intravenously administered cocaine in rhesus monkeys [105–107]. Further, chronic buprenorphine treatment inhibits cocaine-conditioned place preference, suggesting that the reinforcing effects of the drug have been blocked [108]. Buprenorphine, as the sole pharmacotherapeutic agent, has also been shown to significantly decrease cocaine user in heroin abusers [109,110]. However, it has been shown that buprenorphine itself produces conditioned place preference in a dose-related manner, indicating that it may produce reinforcing effects of its own, and that subthreshold doses of cocaine and buprenorphine, given in combination, produce conditioned place preference [111]. Further, this study indicated that cocaine and buprenorphine both increased extracellular levels of dopamine in the nucleus accumbens as measured by microdialysis techniques. Thus, it appears that the reinforcing effects of buprenorphine may substitute for, not inhibit, the reinforcing effects of cocaine, and in this way may produce decreases in operant responding for cocaine in experimental studies. In any case, it seems apparent that opiate related agents may be effective pharmacotherapies for drug abuse. If so, these agents may be effective due to their influences on dopaminergic receptor function, since chronic administration of morphine has been shown to increase brain dopamine receptor numbers [112]. Indeed, the recent identification of the opiate blocker naltrexone as a blocker of alcohol use (see Terenius, this volume) emphasizes these possibilities [113,114].

Conclusions

In summary, there is much evidence which is supportive of a dopamine hypothesis related to reinforcing or addictive properties of psychostimulants. It remains clear that dopaminergic neurons in the mesolimbic region of the brain are essential for mediation of these effects. Research to date, however, suggests that, for reasons that we do not entirely comprehend, it will be difficult to develop potential pharmacotherapeutic agents for the treatment of cocaine abuse which exhibit primary effects only on dopaminergic neurotransmission. It is becoming increasingly clear that other biochemical and behavioural factors must also be taken into account. The relative importance of these other factors in human psychostimulant abusers needs to be clarified. Further, the interactions between the essential elements of drug abuse associated with chronic drug use must be investigated.

References

1. Kuhar, M. J., Ritz, M. C. and Boja, J. W. (1991) Trends Neurosci. **14**, 299–302
2. Koob, G. F. and Bloom, F. E. (1988) Science **242**, 715–723
3. Wise, R. A. and Bozarth, M. A. (1987) Psychol. Rev. **94**, 469–496
4. Wise, R. A. (1978) Brain Res. **152**, 215–247
5. Ritz, M. C., Lamb, R. J., Goldberg, S. R. and Kuhar, M. J. (1987) Science **237**, 1219–1223
6. Bergman, J., Madras, B. K., Johnson, S. E. and Spealman, R. D. (1989) J. Pharmacol. Exp. Ther. **251**, 150–155
7. Grigoriadis, D. E., Wilson, A. A., Lew, R., Sharkey, J. S. and Kuhar, M. J. (1989) J. Neurosci. **9**, 2664–2670

8. Lew, R., Vaughn, R., Simantov, R., Wilson, A. and Kuhar, M. J. (1991) Synapse **8**, 152–153
9. Zaleska, M. M. and Ericinska, M. (1987) Neurosci. Lett. **82**, 107–112
10. Lew, R., Patel, A., Vaughan, R. A., Wilson, A. and Kuhar, M. J. (1992) Brain Res. **584**, 266–271
11. Amara, S. and Kuhar, M. J. (1993) Annu. Rev. Neurosci. **16**, 73–93
12. Shimada, S., Kitayama, S., Lin, C.-L., Patel, A., Nanthakumar, E., Gregor, P., Kuhar, M. J. and Uhl, G. R. (1991) Science **254**, 576–578
13. Kilty, J., Lorang, D. and Amara, S. G. (1991) Science **254**, 578–579
14. Giros, B., Mestikawy, S. E., Bertrand, L. and Caron, M. G. (1991) FEBS Lett. **295**, 149–154
15. Usdin, T. B., Mezey, E., Chen, C., Brownstein, M. J. and Hoffman, B. J. (1991) Proc. Natl. Acad. Sci. U.S.A. **88**, 11168–11171
16. Giros, B., Mestikawy, S. E., Godinot, N., Zheng, K., Han, H., Yang-Feng, T. and Caron, M. G. (1992) Mol. Pharmacol. **42**, 383–390
17. Vandenbergh, D. J., Persico, A. M. and Uhl, G. R. (1992) Mol. Brain Res. **15**, 161–166
18. Boja, J. W., Markham, L., Patel, A., Uhl, G. R. and Kuhar, M. J. (1992) NeuroReport **3**, 247–248
19. Rothman, R. B., Mele, A., Reid, A. A., Akunne, H., Grieg, N., Thurkauf, A., Rice, K. C. and Pert, A. (1989) FEBS Lett. **257**, 341–344
20. Kitayama, S., Shimada, S., Xu, H., Markham, L., Donovan, D. M. and Uhl, G. R. (1992) Proc. Natl. Acad. Sci. U.S.A. **89**, 7782–7785
21. Graybiel, A. M., Moratalla, R. and Robertson, H. A. (1990) Proc. Natl. Acad. Sci. U.S.A. **87**, 6912–6916
22. Persico, A. M., Schindler, C. W., O'Hara, B. F., Brannock, M. T. and Uhl, G. R. (1993) Mol. Brain Res. **20**, 91–100
23. Sharpe, L., Pilotte, N. S., Mitchell, M. and DeSouza, E. B. (1991) Eur. J. Pharmacol. **203**, 141–144
24. Woolverton, W. L. and Johnson, K. M. (1992) Trends Pharmacol. Sci. **13**, 193–200
25. Di Chiara, G. and Imperata, A. (1988) Proc. Natl. Acad. Sci. U.S.A. **85**, 5274–5278
26. Pettit, H. O. and Justice, J. B., Jr. (1989) Pharmacol. Biochem. Behav. **34** 899–904
27. Kalivas, P. W. and Duffy, P. (1990) Synapse **5**, 48–58
28. Hurd, Y. L. and Ungerstedt, U. (1989) Synapse **3**, 48–54
29. Carboni, E., Imperato, A., Perezzani, L. and Di Chiara, G. (1989) Neuroscience **28**, 653–661
30. Bradberry, C. W. and Roth, R. H. (1989) Neurosci. Lett. **103**, 97–102
31. Boja, J. W., Carroll, F. I., Rahman, M. A., Phillip, A., Lewin, A. H. and Kuhar, M. J. (1990) Eur. J. Pharmacol. **184**, 329–332
32. Carroll, F. I., Lewin, A. H., Boja, I. W. and Kuhar, M. J. (1992) J. Med. Chem. **35**, 969–981
33. Cline, E. J., Scheffel, U., Boja, J. W., Carroll, F. I., Katz, J. L. and Kuhar, M. J. (1992) J. Pharmacol. Exp. Ther. **260**, 1174–1179
34. Zelick, N., Angel, I., Paul, S. M. and Kleinman, J. E. (1986) Eur. J. Pharmacol. **126**, 175–176
35. Scheffel, U., Boja, J. W. and Kuhar, M. J. (1989) Synapse **4**, 390–392
36. Canfield, D. R., Spealman, R. D., Kaufman, M. J. and Madras, B. K. (1990) Synapse **6**, 189–195
37. Goeders, N. and Smith, J. (1983) Science **221**, 773–775
38. Roberts, D. C. S., Koob, G. F., Klonoff, P. and Fibiger, H. C. (1980) Pharmacol. Biochem. Behav. **12**, 781–787
39. Roberts, D. C. S. and Koob, G. F. (1982) Pharmacol. Biochem. Behav. **17**, 901–904

40. Martin-Iverson, M. T., Szostak, C. and Fibiger, H. C. (1986) Psychopharmacology **88**, 310–314
41. Lyness, W. H., Friedle, N. M. and Moore, K. E. (1979) Pharmacol. Biochem. Behav. **11**, 553–556
42. Koob, G. F. (1992) Trends Pharmacol. Sci. **13**, 177–184
43. DeWit, H. and Wise, R. A. (1977) Can. J. Psychol. **31**, 195–203
44. Ettenberg, A., Pettit, H. O., Bloom, F. E. and Koob, G. F. (1982) Psychopharmacology **78**, 204–209
45. De la Garza, R. and Johanson, C. E. (1982) Pharmacol. Biochem. Behav. **17**, 1295–1299
46. Wilson, M. C. and Schuster, C. R. (1972) Psychopharmacology **26**, 115–126
47. Goeders, N. E., Dworkin, S. I. and Smith, J. E. (1986) Pharmacol. Biochem. Behav. **24**, 1429–1440
48. Yokel, R. A. and Wise, R. A. (1978) Psychopharmacology **58**, 289–296
49. Risner, M. E. and Jones, B. E. (1976) Pharmacol. Biochem. Behav. **5**, 477–482
50. Davis, W. M. and Smith, S. G. (1975) J. Pharm. Pharmacol. **27**, 540–542
51. Woolverton, W. L., Goldberg, L. I. and Ginos, J. Z. (1984) J. Pharmacol. Exp. Ther. **230**, 678–683
52. Koob, G. F., Le, H. T. and Creese, I. (1987) Neurosci. Lett. **79**, 315–320
53. Woolverton, W. L. (1986) Pharmacol. Biochem. Behav. **24**, 531–535
54. Woolverton, W. L. and Virus, R. M. (1989) Pharmacol. Biochem. Behav. **32**, 691–697
55. Kleven, M. S. and Woolverton, W. L. (1990) Behav. Pharmacol. **1**, 365–373
56. Bergman, J., Kamien, J. B. and Spealman, R. D. (1990) Behav. Pharmacol. **1**, 355–363
57. Callahan, P. M., Piercey, M. F. and Cunningham, K. A. (1992) Psychopharmacology **107**, 73–77
58. Szmigielski, A. and Zalewska-Kaszubska, J. (1991) Neuropharmacology **30**, 259–266
59. Strange, P. G. (1991) Trends Pharmacol. Sci. **12**, 48–49
60. Kumor, K., Scherer, M. and Jaffe, J. (1986) Lancet **ii**, 1341–1342
61. Coffin, V. L., Latranyi, M. B. and Chipkin, R. E. (1989) J. Pharmacol. Exp. Ther. **249**, 769–774
62. Goeders, N. E. and Kuhar, M. J. (1987) Alcohol Drug. Res. **7**, 207–216
63. Fowler, J. S., Volkow, N. D., Wolf, A. P., Dewey, S. L., Schyler, D. J., MacGregor, R. R., Hitzemann, R., Logan, J., Bendriem, B., Gatley, S. J. and Christman, D. (1989) Synapse **4**, 371–377
64. Volkow, N. D., Fowler, J. S., Wolf, A. P., Schyler, D., Shine, C. Y., Alpert, R., Dewey, S. L., Logan, J., Bendriem, B., Christman, D., Hitzemann, R. and Henn, F. (1990) Am. J. Psychiatry **147**, 719–724
65. Volkow, N. D., Hitzemann, R., Wang, G.-J., Fowler, J. S., Wolf, A. P., Dewey, S. L. and Handlesman, L. (1992) Synapse **11**, 184–190
66. Volkow, N. D., Fowler, J. S., Wang, G.-J., Hitzemann, R., Logan, J., Schyler, D. J. and Wolf, A. P. (1992) Synapse, in the press
67. Gawin, F. H., Allen, D. and Humblestone, B. (1989) Arch. Gen. Psychiatry **46**, 322–325
68. Gunne, L. M., Angaard, E. and Jonsson, L. E. (1972) Psychiatr. Neurol. Neurochir. **75**, 225–226
69. Sherer, M. A., Kumor, K. M. and Jaffe, J. H. (1989) Psychiatry Res. **27**, 117–125
70. Gawin, F. H. (1986) Psychopharmacology **90**, 142–143
71. Gawin, F. H., Morgan, C., Kosten, T. R. and Kleber, H. D. (1989) Psychopharmacology **97**, 402–403
72. Weddington, W. W., Jr., Brown, B. S., Hartsen, C. A., Hess, J. M., Mahaffey, J. R., Kolar, A. F. and Jaffe, J. H. (1991) Am. J. Drug Alcohol Abuse **17**, 137–152

73. Kosten, T. R., Morgan, C. M., Falcione, J. and Schottenfeld, R. S. (1992) Arch. Gen. Psychiatry **49**, 894–898
74. Arndt, I. O., Dorozynsky, L., Woody, G. E., McLellan, A. T. and O'Brien, C. P. (1992) Arch. Gen. Psychiatry **49**, 888–893
75. Clow, D. W. and Hammer, R. P. (1991) Neuropsychopharmacology **4**, 71–75
76. Preston, K. L., Sullivan, J. T., Strain, E. C. and Bigelow, G. E. (1992) J. Pharmacol. Exp. Ther. **262**, 279–291
77. Chait, L. D., Uhlenhuth, E. H. and Johanson, C. E. (1987) J. Pharmacol. Exp. Ther. **242**, 777–783
78. Pogun, S., Scheffel, U. and Kuhar, M. J. (1991) Eur. J. Pharmacol. **198**, 203–205
79. Wilson, M. C. and Schuster, C. R. (1976) Pharmacol. Biochem. Behav. **4**, 207–210
80. Risner, M. E. and Silcox, D. L. (1981) Psychopharmacology **75**, 25–30
81. Sellers, E. M., Busto, M. and Kaplan, H. L. (1989) in Testing for Abuse Liability of Drugs in Humans (Fischman, M. W. and Mello, N. K., eds.), NIDA Res. Monogr. No. 92
82. Foltin, R. W. and Fischmann, M. W. (1991) J. Pharmacol. Exp. Ther. **257**, 247–261
83. Ritz, M. C. and Kuhar, M. J. (1989) J. Pharmacol. Exp. Ther. **248**, 1010–1017
84. Lecesse, A. P. and Lyness, W. H. (1984) Brain Res. **303**, 153–162
85. Lyness, W. H. (1983) Subt. Alcohol Actions Misuse **4**, 305–312
86. Smith, F. L., Yu, D. S. L., Smith, D. G., Lecesse, A. P. and Lyness, W. H. (1986) Pharmacol. Biochem. Behav. **25**, 849–855
87. Yu, D. S. L., Smith, F. L., Smith, D. G. and Lyness, W. H. (1986) Life Sci. **39**, 1383–1388
88. Carroll, M. F., Lac, S. T., Asencio, M. and Kragh, R. (1990) Psychopharmacology **100**, 293–300
89. Porrino, L. J., Ritz, M. C., Sharpe, L. G., Goodman, N. L., Kuhar, M. J. and Goldberg, S. R. (1989) Life Sci. **45**, 1529–1535
90. Loh, E. A. and Roberts, D. C. S. (1990) Psychopharmacology **101**, 262–266
91. Roberts, D. C. S. (1991) in Cocaine: Pharmacology, Physiology and Clinical Strategies (Lakoski, J. M., Galloway, M. P. and Galloway, F. J., eds.), The Telford Press, U.K.
92. Gawin, F. H., Riordan, C. and Kleber, H. D. (1985) Am. J. Drug Alcohol Abuse **11**, 193–197
93. Ritz, M. C. and George, F. R. (1993) J. Pharmacol. Exp. Ther., in the press
94. Cunningham, K. A. and Callahan, P. M. (1991) Psychopharmacology **104**, 177–180
95. Fischman, M. W., Foltin, R. W., Nestadt, G. and Pearlson, G. D. (1990) J. Pharmacol. Exp. Ther. **253**, 760–770
96. McElroy, S. L., Weiss, R. D., Mendelson, J. H., Teoh, S. K., McAfee, B. and Mello, N. K. (1990) in Problems of Drug Dependence 1989 (Harris, L. S., ed.), NIDA Res. Monogr. No. 95, pp. 57–63, U.S. Government Printing Office, Washington, D.C.
97. Kuhn, K. L., Halikas, J. A. and Kemp, K. D. (1989) NIDA Res. Monogr. **95**, 316–317
98. Hatsukami, D., Keenan, R., Halikas, J., Pentel, P. R. and Hartman Brauer, L. (1991) Psychopharmacology **104**, 120–124
99. Goeders, N. E., McNulty, M. A., Mirkis, S. and McAllister, K. H. (1989) Pharmacol. Biochem. Behav. **33**, 859–866
100. Goeders, N. E. (1991) J. Pharmacol. Exp. Ther. **259**, 574–581
101. Goeders, N. E., Bell, V., Guidroz, A. and McNulty, M. A. (1990) Brain Res. **515**, 1–8
102. Finlay, J. M., Damsma, G. and Fibiger, H. C. (1992) Psychopharmacology **106**, 202–208
103. McAllister, K., Goeders, N. and Dworkin, S. (1988) NIDA Res. Monogr. **81**, 101–108
104. Koe, B. K., Kondratas, E. and Russo, L. L. (1987) Eur. J. Pharmacol. **142**, 373–384

105. Mello, N. K., Mendelson, J. H., Bree, M. P. and Lukas, S. E. (1989) Science **245**, 859–861
106. Mello, N. K., Mendelson, J. H., Bree, M. P. and Lukas, S. E. (1990) J. Pharmacol. Exp. Ther. **254**, 926–939
107. Mello, N. K., Mendelson, J. H., Bree, M. P. and Lukas, S. E. (1992) J. Pharmacol. Exp. Ther. **260**, 1185–1193
108. Kosten, T. A., Marby, D. W. and Nestler, E. J. (1991) Life Sci, **49**, 201–206
109. Kosten, T. R., Kleber, H. D. and Morgan, C. (1989) Biol. Psychiatry **26**, 637–639
110. Kosten, T. R., Kleber, H. D. and Morgan, C. (1989) Life Sci. **44**, 887–892
111. Brown, E. E., Finlay, J. M., Wong, J. T. F., Damsma, G. and Fibiger, H. C. (1991) J. Pharmacol. Exp. Ther. **256**, 119–126
112. Martin, J. R. and Takemori, A. E. (1986) Eur. J. Pharmacol. **121**, 221–229
113. Volpicelli, J. R., Alterman, A. I., Hayashida, M. and O'Brien, C. P. (1992) Arch. Gen. Psychiatry **49**, 876–880
114. O'Malley, S. S., Jaffe, A. J., Chang, G., Schottenfeld, R. S., Meyer, R. E. and Rounsaville, B. (1992) Arch. Gen. Psychiatry **49**, 881–887

Biochem. Soc. Symp. **59**, 65–81
Printed in Great Britain

Drugs of abuse: biochemical surrogates of specific aspects of natural reward?

Gaetano Di Chiara, Elio Acquas, Gianluigi Tanda and Cristina Cadoni

Department of Toxicology, University of Cagliari, Viale A. Diaz 182, 09100 Cagliari, Italy

Synopsis

In this paper it is argued that drugs of abuse act on specific neurotransmitter pathways and by this mechanism elicit neurochemical changes that mimic some aspects of the overall pattern of the neurochemical effects of natural rewarding stimuli. Thus, drugs of abuse are biochemically homologous to specific aspects of natural rewarding stimuli. The behavioural similarity between drugs of abuse and natural stimuli, including that of being rewarding, results from their common property of activating neurochemically specific pathways. Natural stimuli accomplish this result indirectly through their sensory properties and incentive learning while drugs stimulate by a direct central action the critical reward pathways. Many drugs of abuse mimic the incentive properties of natural stimuli and their ability to stimulate mesolimbic dopamine pathways (Fig. 1). Both natural rewards and drugs of abuse, including amphetamine, cocaine and other psychostimulants, preferentially stimulate dopamine transmission in the mesolimbic nucleus accumbens compared with the dorsal caudate, an area related to the extrapyramidal motor system. Although many drugs of abuse mimic the incentive aspect of natural reward, this is probably not an absolute prerequisite for conferring to a drug some abuse liability. It might be predicted that certain drugs might be abused as a result of their action at sites located beyond dopamine or by mimicking other aspects of naturally rewarding stimuli such as the 'functional' (or trophotropic). This might be the case with opiates (which also mimic the 'incentive' aspect) and of benzodiazepines, as a result of activation of the central opioid reward system and of the central γ-aminobutyric acid (GABA)–benzodiazepine system respectively. The hypothesis appears to have heuristic value as it predicts that biochemical mechanisms important for the rewarding properties of drugs of abuse are expected to play a role also in natural reward. One test of this hypothesis is offered by the observation that the 5-hydroxytryptamine (5-HT) system, through 5-HT_3 receptors, and the central opioid system, through δ-opioid receptors, can contribute to the mechanism of the dopamine-activat-

ing properties of certain drugs of abuse. On this basis it would be predicted that drugs acting on 5-HT_3 and on δ-opioid receptors would interfere with or mimic certain aspects of natural rewarding stimuli.

Introduction

A basic property of drugs of abuse is that of promoting behaviours that tend to increase the probability of coming into contact with the drug leading to drug seeking behaviour [1] (see chapter by Stolerman, this volume).

In fact drugs of abuse are rewarding and their action results in feelings of pleasure or reduction of dysphoria and anxiety that correspond to the subjective reports of 'high', 'euphoria' and 'relaxation' after their acute administration.

To clarify the mechanism of the positive reinforcing properties of drugs of abuse, two premises can be made. The first is that drugs do not invent anything but simply act on mechanisms and processes that the organism utilizes during its normal functioning. The second is that biological mechanisms are the result of a developmental history (phylogenesis) having the goal of improving the adaptation of the organism to the environment, thus ensuring survival of the species. In view of this, understanding a biological process should also involve the appraisal of its phylogenetic significance.

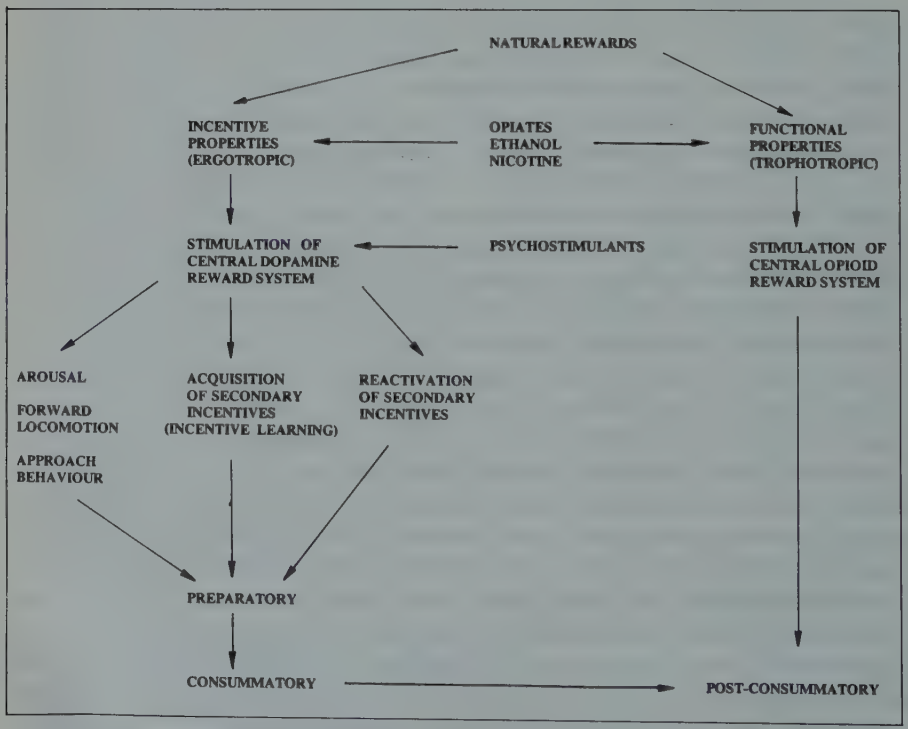

Fig. 1. Neurochemical substrates of the rewarding properties of natural stimuli and of their drug surrogates.

Here it will be argued that drugs of abuse act by primarily activating chemically specific neural pathways that are physiologically stimulated by natural rewarding stimuli essential for survival of the self and of the species. This hypothesis can account for many of the properties of these drugs including their ability to induce psychological dependence and craving, and can in turn generate new predictions on the neurochemistry of natural reward.

Natural reward: ethology and neurochemistry

Feeding, drinking, and sexual and maternal behaviour are directed towards goals essential for the survival of the self and of the species; in order to ensure the accomplishment of these behaviours, natural selection has provided the brain of higher phyla with centres that are sensitive to survival-related stimuli and are capable of reacting to their contact with a positive emotional response. Thus, natural stimuli such as food, water, sex and mother and newborn interactions are rewarding.

Three phases can be distinguished in naturally rewarded behaviour: a preparatory (or anticipatory), a consummatory and a post-consummatory phase [2,3]. These three phases are well exemplified in eating behaviour. Food, the natural rewarding stimulus, is provided with distinctive sensory properties (smell, colour, texture, taste) that readily stimulate arousal, forward locomotion and approach behaviour. This preparatory phase is finalized to and eventually followed by successful contact with the rewarding stimulus and its 'consumption'; the consummatory phase thus describes the direct interaction with the rewarding stimulus in order to utilize its survival-related properties. Accordingly, eating, drinking, copulating and nursing are consummatory phases while search for food and water or sex, are preparatory phases of naturally rewarded behaviour.

The properties of natural rewarding stimuli can be defined on the basis of the changes they induce in the organism. Naturally rewarding stimuli seem to have two main properties, an 'incentive' [4,5], appetitive property, and a 'functional' property (Fig. 1). In the case of food, its smell, sight and taste are incentive properties while its metabolic and caloric properties are the functional ones. In a female her sex-attracting properties are the incentive while her ability to promote male ejaculation could be regarded as the functional property. Thus, the incentive aspects of natural reward are essential for stimulating behaviour directed to approach and contact with the rewarding stimulus [4,5]. The incentive properties of natural reward also increase the probability of contact with the primary reward by conferring, through conditioning, incentive properties to otherwise neutral environmental stimuli ('incentive learning') [4,5]; moreover, incentive properties are important during consummatory phases of behaviour for maintaining the contact with the stimulus and completing its consumption. Instead, the functional properties of natural rewards are essential for their effectiveness in biological and physiological terms. Not only the 'incentive' but also the 'functional' properties of the natural stimulus are likely to contribute to their reinforcing properties.

However, since the 'functional' properties of natural rewards are related to maintenance of homeostasis, it is likely that their reinforcing properties arise from their ability to reconstitute a perturbed physiological environment [6]. 'Drive states' (hunger, thirst, etc.) arising from a perturbed physiological condition are able to increase the

incentive value of natural rewards [4]. Since the functional properties of natural rewards are able to reduce drive, they can control behaviour indirectly through their influence on the incentive value of natural rewards.

The 'incentive' and 'functional' properties of natural rewards are related to different physiological changes; thus the incentive aspects promote ergotropic changes [7] characterized by arousal, activation of motor activity and of the sympathetic nervous system, release of corticosteroids and catabolism, while the 'functional' aspects promote trophotropic changes [7] such as activation of the parasympathetic nervous system, insulin release, anabolism, sedation, rest, and eventually sleep. Satiety could be regarded as a typically trophotropic state promoted by the 'functional' properties of natural reward. Viewed from this perspective a description of the physiological properties of natural rewarding stimuli might be simply, following Hess [7], that of ergotropic (incentive) and trophotropic (functional) properties (Fig. 1).

From the above definitions it appears that the two properties of natural rewarding stimuli might express themselves in more than one phase of naturally rewarded behaviour. Thus, it is likely that the 'incentive' aspects of natural reward operate mainly during the 'preparatory' but also during the early 'consummatory' phase. However, it is also likely that the 'functional', metabolic and drive-reducing properties of natural rewards operate mainly during the late 'consummatory' and 'post-consummatory' phases of rewarded behaviour (Fig. 1).

Activation of mesolimbic dopamine as a marker of the 'incentive' properties of natural reward

Anatomical, pharmacological and neurochemical studies indicate that naturally rewarded behaviour is related to the activity of phylogenetically old centres that constitute the limbic system. Within this system several neurochemically specific pathways appear to play a role in natural reward and, in particular, the mesolimbic and mesocortical pathways that release dopamine as a neurotransmitter [8] (Fig. 2), the long hypothalamo-mesencephalic and short intrinsic neurons releasing opioid peptides (β-endorphin, enkephalins and dynorphins), and the long and short neurons releasing GABA as an inhibitory transmitter [9].

These different neurotransmitter systems (dopamine, opioid peptides and GABA) might mediate different aspects of natural reward. The 'incentive' aspect of natural reward might be related to an activation of dopamine transmission in the mesolimbic system and in particular in the nucleus accumbens septi (Fig. 2). In fact it has been recently reported that natural rewarding stimuli such as food and sex preferentially stimulate the release of dopamine, as measured by brain microdialysis, in the nucleus accumbens of rats [10]. According to Phillips *et al.* [10] stimulation of dopamine transmission in the nucleus accumbens would be mostly related to the preparatory phase of natural reward. In contrast with this hypothesis, however, stimulation of dopamine transmission in the nucleus accumbens, as measured by brain microdialysis, seems to take place also during the consummatory phase both in sexual [11] and in eating behaviour [12]. It might be argued that this is an artifact of microdialysis, related to the delay involved in the diffusion of dopamine from release sites to the extracellular compartment and the time necessary for changes in the extracellular dopamine pool to take place. However, rather than being related to a specific phase of naturally rewarded behaviour, it is entirely possible that the stimulation of dopamine transmission is related

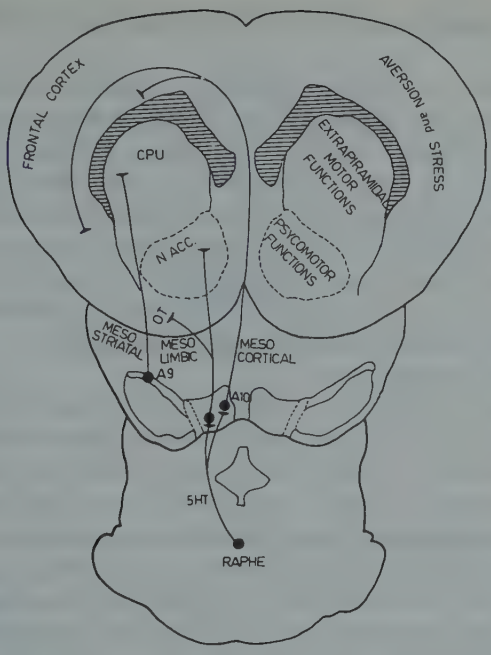

Fig. 2. Dopamine neurons ascending to the forebrain and their possible behavioural significance. CPU, caudate-putamen; N.ACC., nucleus accumbens; O.T., olfactory tubercle. Reproduced from [56] with permission.

to a specific property of natural rewards, such as the 'incentive' property, that is likely to act across the preparatory as well as the consummatory phase (Fig. 1).

Indeed, activation of the mesolimbic dopamine system accounts for most of the recognized properties of the incentive aspect of natural rewarding stimuli namely: (1) the ability to elicit arousal and forward locomotion; (2) the ability to promote acquisition by neutral environmental stimuli of the response-eliciting properties of the natural rewards (primary reinforcers; by this process, 'incentive learning', otherwise neutral environmental stimuli become capable of acting as reinforcers, secondary reinforcers) [13]; (3) the ability to increase or reactivate the incentive properties of secondary reinforcers [4,14–16] (Fig. 1).

Stimulation of the central opioid reward system has been related to the drive-reducing (functional) aspect of natural reward but such a precise relationship is at the moment purely conjectural [17] (Fig. 1). It is well-established, however, that blockade of opioid receptors interferes with food reward [18] as well as with intracranial self-stimulation from specific brain sites different from those corresponding to the dopamine pathways [19]. As for the possible role of GABA neurons in natural reward, the evidence is mainly indirect and derives from studies on the effects of drugs active on GABA-ergic transmission and in particular on benzodiazepine receptor ligands [9,20].