Neuropharmacology, Vol. 18, pp. 963 to 969
Pergamon Press Ltd 1979. Printed in Great Britain

REINFORCING STIMULUS PROPERTIES OF DRUGS

J. M. VAN REE
Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Vondellaan 6, 3521 GD Utrecht, The Netherlands

Summary—The reinforcing efficacy of psychoactive drugs can reliably be studied in experimental animals by using procedures for drug self-administration. This property of drugs is used to predict qualitatively and quantitatively their abuse potential in humans. External factors like the dose of the drug, the schedule of drug availability and stimulus control are critically important in initiation, maintenance and cessation of self-administering behaviour. Drug-induced changes in the organism, including tolerance and physical dependence, may contribute more or less to the behaviour associated with drug use and consequently change the pattern of drug intake. Concerning the internal factors involved in the process by which a given drug consequence gains control over behaviour, it is suggested that addictive drugs may mimic the action of endogenous substances which are implicated in the physiological mechanisms underlying reinforcement. Neuropeptides e.g. those related to vasopressin, which are involved in the adaptation of the individual to his environment, may modulate the consequences of drug self-administration by interfering with the complex interaction of addictive drugs with brain homeostatic mechanisms. It is postulated that derangements in neuropeptide systems may be critical factors in the development of addictive behaviour.

Drugs are considered as psychoactive when they can be used to affect the central nervous system and as a consequence the behavior of individuals. Many naturally occurring substances, mainly of plant origin, can be regarded as psychoactive drugs. In the crude form, these substances have been used for many centuries to influence the brain function of healthy individuals as well as of mentally disturbed patients. Outside the medical setting, these drugs are self-administered mainly for their euphoric effects. Once achieved, the euphoria may be the incentive to repeated administration of the drug, even when the sacrifice of other behaviours is required. This may lead to a state of drug dependence characterized by the drug user performing substantial amounts of behaviour leading specifically to further administration of the drug (Kalant, Engel, Goldberg, Griffiths, Jaffe, Krasnegor, Mello, Mendelsohn, Thompson and van Ree, 1978). Severe degrees of dependence are commonly labelled as addiction, particularly in clinical practice. Historically, studies on the addictive properties of drugs in experimental animals, have mainly been focused on morphinomimetics and ethanol. These drugs also induce physical dependence, characterized by a specific pattern of biological events which occur in response to withdrawal of the drug. Physical dependence has been considered for many years as one of the most important mechanisms underlying drug addiction. However, as will be discussed below in detail, recent research has not substantiated this assumption.

The concepts of operational analysis of behaviour formulated by Skinner (1938) have had important consequences for the experimental analysis of drug dependence. Apart from technological contributions (e.g. the use of the so-called Skinner box), a conceptual frame-work emerged which allows the study of the relation between drug administration by organisms and the behavioural consequences of drug administration, particularly when the administration is contingent on the occurrence of a prior response of the organism. An experimental situation in which the subject is given the opportunity to take the drug has been called drug self-administration. A drug serves as reinforcer when the occurrence of the behavioural pattern which is followed by drug administration increases or is maintained. Drug reinforcement belongs to a large class of other reinforcing events such as food and water presentation and electrical brain stimulation. Comparing the interaction of the various reinforcers, of the organism and of its environment, allows generalization about the control of drug reinforcers over behaviour to be applied to other reinforcers. The basic mechanisms underlying drug dependence may thus become clearer and procedures then devised to eliminate the control that drugs can establish over behaviour. For the present survey, the terms reward and reinforcement will be used interchangeably, although some psychologists have argued that the term reward has more bearing on the specific subjective effects of the drug and hence should not be used in relation to non-human subjects.

DRUG REINFORCEMENT

In 1940 Spragg suggested that drugs could serve as reinforcers for behaviour (Spragg, 1940). The basis for this suggestion was that chimpanzees previously made physically dependent on morphine, could learn to select one of two boxes concealing a syringe filled with a morphine solution which would subsequently be administered to the animal by the experimenter. Self-injection by animals was first reported in 1955 by Headlee, Coppock and Nichols (1955). These authors

demonstrated that morphine was injected intraperitoneally by physically dependent rats. Techniques for intravenous self-administration by both monkeys and rats were developed in the early sixties (Weeks, 1962; Denau, Yanagita and Seevers, 1969; Schuster and Thompson, 1969). These techniques have been widely used for detailed analyses of the reinforcing properties of drugs. In a typical experiment, an animal is given access to a device which when manipulated appropriately delivers an intravenous injection of the drug according to a specific reinforcement schedule. In terms of operational analysis of behaviour, appropriate manipulation of the device is the response and the subsequent injection, the reinforcement. Although intravenous self-administration in rats and monkeys is the most frequently used, other models of drug self-administration have been developed as well. These models involve a variety of species (e.g. cat, dog), routes of drug administration (e.g. intragastric, oral, inhalation, intracerebroventricular) and types of devices (e.g. levers) (Schuster and Thompson, 1969; Thompson and Pickens, 1969; Kalant *et al.*, 1978).

Using these models, it has become increasingly clear that there are many drugs, from several pharmacological classes, which can serve as reinforcing stimuli in animal experiments (Schuster and Thompson, 1969; van Ree, Slangen and de Wied, 1974). However, the various drugs differ in the ease with which they can generate for example intravenous self-administering behaviour. This behaviour is readily induced by various morphinomimetics (e.g. heroin, fentanyl) and psychomotor stimulants (e.g. amphetamine, cocaine), which may indicate that these drugs act very strongly as reinforcers. Other compounds such as chlorpromazine and some opiate-antagonists do not easily generate self-administration, suggesting that these drugs reinforce only very weakly, if at all. There is good evidence that man has abused to some extent most of the drugs that initiate and maintain self-administering behaviour in laboratory animals and which are used by man. Conversely, psychoactive drugs which fail to initiate and maintain self-administration are not readily abused by humans. Thus, the reinforcing efficacy of a drug may predict, at least qualitatively, the abuse potential of this drug in humans. Methods have recently been developed for comparing the relative reinforcing efficacy of drugs. Some of these procedures seem promising for making quantitative predictions of the abuse potential, of at least one class of psychoactive drugs (Thompson and Young, 1978).

The self-administration techniques have thus proved to be the most consistent and reliable predictors of abuse potential in man (Thompson and Unna, 1977). In fact, drugs with a high abuse potential are those which have properties leading to their self-administration under various conditions in experimental animals. Further research will show whether this predictive value will apply to new classes of drugs as well.

EXTERNAL ENVIRONMENTAL FACTORS

External factors affecting the initiation, maintenance and cessation of self-administration have been well reviewed (Schuster and Thompson, 1969; Weeks, 1975; Thompson and Pickens, 1975; Kalant *et al.*, 1978). Most of the research concerns those factors that can readily be manipulated by the experimenter, e.g. the dose of drug, the schedule of drug availability and stimulus control.

Virtually all the pharmacological responses are a function of the dose delivered. Thus, it is not surprising that the dose of a drug should be important for self-administering behaviour. An intermediate dose range is optimal for the initiation of this behaviour and very low and very high doses do not favour it. Varying the unit dose delivered per injection after the animal had acquired the behaviour, showed that, in general, increases in unit dose produced increases in total drug intake for most drugs in both human and experimental animals (Weeks and Collins, 1964; Wilson, Hitomi and Schuster, 1971; Griffiths and Bigelow, 1978; Harrigan and Downs, 1978). This relationship was somewhat less pronounced with psychomotor stimulants (Yokel and Pickens, 1973). When very low doses were tested, a progressive decrease of drug intake was found. It follows, that when a wide range of doses was examined, the total number of infusions varied as an inverted U-shaped function. Similar data were obtained when rats were exposed to graded unit doses of morphine, heroin and fentanyl during the acquisition of the behaviour (van Ree, Slangen and De Wied, 1978a). The doses used in this study were in the intermediate range. The number of responses per 24 hr was almost equal for the various unit doses. However, the total daily drug intake was related to the unit dose in that a higher drug dosage led to more drug intake. Thus, the unit dose delivered is one of the factors which determine the ultimate level of drug intake in self-administration. The amount of the drug taken can thus serve as a useful index of the reinforcing efficacy of the reinforcer i.e. drug injection. The extinction of self-administration also is somewhat influenced by the drug dose delivered before extinction. Several narcotics (van Ree *et al.*, 1974) and amphetamine (Thompson and Pickens, 1975) increased the time to extinction as a function of the dose. The resistance to extinction of morphine self-administration appeared to be proportional to the intensity of previous dependence (Carnathan, Mayer and Cochin, 1977). Since the disappearance of an instrumental response during extinction may give some clue about the strength of the response and the strength of the response is dependent among other things on the strength of the reinforcer, the extinction data suggest that the reinforcing potential is increased when the unit dose increases. This possibility is consistent with the conclusion drawn from the relation between actual drug intake and unit dose.

Another variable frequently studied during main-

tenance of drug self-administration is the schedule of drug availability. In general, the characteristics of the schedule controlled behaviour maintained by drug reinforcers cannot be distinguished from the characteristics of behaviour maintained by non-drug reinforcers (Thompson and Pickens, 1975; Kelleher and Goldberg, 1975; Spealman and Goldberg, 1978). Responses to variation in the schedule can show to what extent the behaviour is being controlled by drug reinforcement. The "response cost" in terms of the amount of work that individuals will expend to earn drug reinforcement is of particular interest. Both animals and humans decreased drug self-administration as the response requirement was increased (Griffiths and Bigelow, 1978). Procedures in which an increasing number of responses are required to obtain a drug infusion termed "progressive ratio" procedures indicated that the breaking point—the response requirement that the animal fails to meet—depends on the dose and on the drug itself. The breaking point was increased when the dose of the drug was increased, an effect possibly related to the higher reinforcing value of a higher dose. Furthermore, the rank order for the comparison of the breaking points of various stimulants and of different narcotics, correlates highly with their reported dependence liability in man (Brady and Griffiths, 1976; Hoffmeister, 1979).

Although the primary reinforcing properties of drugs are the most important stimuli in drug self-administration, other stimuli may also acquire the ability to control the probability of further drug intake. Neutral environmental stimuli can become conditioned reinforcers when they are paired repeatedly with drug reinforcement. When conditioned stimuli are scheduled intermittently between drug injections, the amount of drug intake is substantially increased (Goldberg and Tang, 1977). These conditioned stimuli may be important in the etiology of the relapse of drug abuse since the environment in which the drug was previously taken may play a significant role in relapse. No data are yet available to support this hypothesis. Discriminative stimuli may also gain control over behaviour. These stimuli signal the occasions on which the appropriate behavioural pattern can lead to drug reinforcement. Discriminative stimuli have been used in so-called second order schedule conditions, in which long sequences of response behaviour are maintained by presentation of these stimuli, although the drug reinforcement is presented only intermittently. Such schedules may be useful for analyzing drug-seeking behaviour, as they minimize the effect of frequent drug administration on response rate. Moreover, human drug-seeking behaviour also seems to be controlled to some extent by discriminative stimuli. Internal cues elicited by drug injection may gain control over behaviour (Colpaert, 1977, 1978). This discriminative complex has been much studied in experimental animals and has been proposed as model system for evaluating those characteristic subjective effects of drugs, which play a profound role in initiating and maintaining drug seeking behaviour in man (Fraser, Van Horn, Martin, Wolbach and Isbell, 1961).

Other environmental factors which may be of significance for initiating and maintaining drug-reinforced behaviour have only been studied occasionally. The environmental conditions under which the drug is taken, e.g. social conditions and aversive conditions, will certainly influence drug taking behaviour. Other non-drug reinforcers will interact or even contribute to drug seeking behaviour. It has been reported that dominance hierarchy influenced the amount of alcohol intake (Cadell and Cressman, 1972). Drug injections may or may not gain and maintain control over behaviour in a particular individual depending on a wide range of historical variables, e.g. a pre-existing behaviour repertory.

Most of these external environmental factors are more or less involved in the procedures used to eliminate drug-seeking behaviour. In animals, extinction can be produced by removing the self-administered drug from the infusion fluid. Blocking the reinforcing effects of drugs taken by humans may lead to the extinction of drug-seeking behaviour. The practice of giving the narcotic antagonist naloxone to narcotic addicts and α-methyl-*para*-tyrosine to amphetamine users is based on this idea. Although this principle of treatment is valid, the actual outcome is so far not impressive. Another approach is to supply aversive stimuli linked to and simultaneous with the self-administered drug as a part of punishment or conditioned aversive procedures. An example of such procedures is the disulfiram therapy of alcoholics, which results in acetaldehyde poisoning when the user continues to ingest alcohol. To date the results obtained have not been much more satisfactory than with the other procedures. It may be possible to decrease stimulus control on drug-seeking behaviour by weakening the influence which environmental cues exert: either the response cost can be manipulated or alternative reinforcers can be presented. Although the experimental data so far favour these possibilities (Griffiths and Bigelow, 1978), more research is needed before procedures like these are ready for clinical application. That a high drug dose is more reinforcing than a lower dose may contribute to the partial success of the methadone detoxification program for patients with a moderate degree of heroin addiction. This programme involves gradually decreasing the daily methadone dose.

DRUG-INDUCED CHANGES IN THE ORGANISM

The self-administered drug may alter a variety of homeostatic mechanisms. These changes may contribute more or less to the behaviour associated with drug use. First, these drug-induced changes may alter the reinforcing properties of self-administered drugs. The changes include alterations in mood (euphoria or

dysphoria), in social behavioural interactions, in sexual and in aggressive behaviour (Mello and Mendelson, 1978). These subjective and objective effects induced by the drug may themselves reinforce the drug-seeking behaviour. In experimental animals, the subjective i.e. desirable effects may at least partly be analyzed by investigating the cueing properties of the drug (Colpaert, 1977). Second, the development of adaptive changes in response to repeated administration of the drug may be important for the behavioural pattern associated with drug taking. The development of tolerance and physical dependence is of particular interest.

The development of tolerance is characterized by decreased effectiveness of a given dose of drug when administered repeatedly because of a change in the dose-response curve (Kalant, 1978). Adaptive changes involved in tolerance development are alteration in drug bioavailability in the central nervous system (CNS) due to e.g. increased biotransformation or decreased brain penetration, and, more interesting for the present survey, adaptations in the CNS subsequent to activation of the drug receptor complex. Tolerance can develop to many psychoactive drugs including various addictive drugs. If tolerance development is due to an altered drug bio-availability in the CNS, all central activities of the drug, including its reinforcing properties will be diminished. This will have as consequence increased drug intake and enhanced drug-seeking behaviour. However, tolerance to most addictive drugs develops on the basis of adaptive changes in the CNS as can be inferred from the selectivity of development, i.e. only some actions of the drug are subjected to tolerance development. Interestingly, little or no tolerance appears to develop to the reinforcing effects and to the discriminative internal stimuli of drugs (Kalant, 1978; Colpaert, 1978). The acquisition of heroin self-administration was not significantly affected by manipulations aimed at inducing tolerance (van Ree *et al.*, 1978a). This supports the idea that tolerance is not critically involved in the etiology of self-administering behaviour (Weeks and Collins, 1968; Woods and Schuster, 1971; van Ree *et al.*, 1978a). The degree of self-administering behaviour is determined by the balance between effects which enhance the drug-induced response (e.g. reinforcing activity and motor increasing effects) and effects which decrease the drug-induced response (e.g. aversive and motor impairing effects). Consequently, when the selective tolerance developed is to the response decreasing effects, the amount of drug taken may increase. Depending on drug availability, this could be achieved by increasing the unit dose per injection. In turn, this may lead to more drug intake, as can be inferred from the relationship between the unit dose delivered and the ultimate level of drug intake. Also whether drug intake is increased by using higher doses or by more frequent administration of the drug, there may be enhanced risks of toxicity, increased untoward effects, more drug seeking behaviour (including that related to the higher costs) and a higher level of tolerance.

Physical dependence can be defined as an altered state which is induced by repeated administration of a drug and recognizable by a specific pattern of disturbances on withdrawal of the drug. Most concepts to explain physical dependence in particular with respect to morphinomimetics and ethanol suggest that the development of physical dependence covaries with the development of tolerance although there are exceptions (Kalant, 1978). The experiments outlined above and which aimed at finding the role of tolerance in self-administration, suggested that physical dependence was not significantly involved in the acquisition of self-administering behaviour. However, the withdrawal syndrome seen on stopping the drug intake of physically dependent organism may contribute to the maintenance or re-evocation of self-administering behaviour. The termination by further drug intake of the aversive internal states as happens during the withdrawal of some drugs, may acquire reinforcing value. These may then result in more frequent administration of the drug and consequently a higher drug intake.

In conclusion, neither tolerance nor physical dependence play a primary role in the acquisition of drug self-administration, but both may contribute to the maintenance of drug intake and to its level. This is consistent with the observation that the therapeutic use of drugs with a high abuse potential induces drug-seeking behaviour in only a limited number of patients.

INTERNAL FACTORS

There are only few data concerning the internal factors involved in drug self-administration. Two types of such factors may be distinguished. First, the neuronal substrates affected by addictive drugs and which, when activated produce reinforcement. Second, factors that modulate the drug-induced reinforcing activity. Both factors may be critical for the initiation of self-administration and may contribute to the individual variations in susceptibility to addictive drugs with respect to drug-taking behaviour.

Little is known about the neural-anatomical substrate for drug reinforcement. There are behavioural similarities between drug self-administration and brain electrical self-stimulating behaviour. It has been hypothetized that neuronal processes which mediate the positively reinforcing characteristics of drugs which produce dependence, are also involved in self-stimulation (Esposito and Kornetsky, 1977; Maroli, Tsang and Stutz, 1978). Evidence has been presented that there is a dopamine system in the brain that plays a critical role in the reinforcing effects of both self-administration of some drugs and brain self-stimulation elicited from certain brain structures (Wise, 1978). However, it is not clear yet whether a dopamine reward substrate is involved in the action

of all drugs when they are self-administered and in all rewards of brain stimulation.

It has been postulated that the brain contained sites which recognize a drug in a specific way (receptors). The drug would then have affinity for these receptors and in some cases could activate the receptor complex (intrinsic activity), which in turn would mediate the biological effects. Both the reinforcing effects and the discriminative internal stimuli of morphinomimetics may be mediated by receptors because of stereospecificity and of the inhibiting effects of specific opiate antagonists. *In vitro* studies using various brain preparations indicate that morphine and other psychoactive drugs have an affinity for specific brain binding sites. This affinity suggested the hypothesis that the brain contained endogenous ligands for the specific binding sites. With respect to morphinomimetics, these ligands have recently been isolated and subsequently identified. They are called endorphins (endogenous morphine) and most are structurally related to the pituitary hormone β-lipotropin. There is evidence that various endorphin-containing pathways exist in the brain. There are various short pathways containing enkephalins (endorphins with 5 amino acids) and a long pathway, with cell bodies in the hypothalamic arcuate nucleus and containing β-lipotropin and β-endorphin (an endorphin with 31 amino acids) (Hökfelt, Elde, Johansson, Terenius and Stein, 1977; Watson, Akil, Berger and Barchas, 1979). The presence of endorphins in pituitary and brain has raised the question of whether these entities are involved in self-administration. These endogenous substances may be involved in the functioning of physiological systems which are also susceptible to narcotic drugs. Indeed, enkephalins and specially leu-enkephalin, were found to induce self-administering behaviour when given intracerebroventricularly (Belluzzi and Stein, 1977; Stein and Belluzzi, 1978). Although self-administration of met-enkephalin could not be reproduced, β-endorphin appeared to share the abuse liability of heroin, in that rats worked for a response-contingent intracerebroventricular injection when they received relatively low amounts of β-endorphin (van Ree, Dorsa and Colpaert, 1978c; van Ree, Smyth and Colpaert, 1979). This suggests that β-endorphin and other endorphins can act as positive reinforcers and may be involved in the physiological processes underlying reward. Other data suggest that β-endorphin also possesses discriminative internal stimulus properties similar to those of narcotic drugs (van Ree *et al.*, 1979). Both the positive reinforcing and the discriminative stimulus properties of β-endorphin indicate that this peptide may exert powerful control over behaviour. Narcotic drugs may mimic these actions of β-endorphin and in this way control behaviour to such an extent that the functioning of the organism becomes conditional upon these drugs. This may lead to the postulate that altered bio-availability of endorphins may be a critical factor in the development of narcotic abuse. Whether endorphins can also be implicated in the reinforcing effects of other self-administered drugs, remains to be shown. Interestingly, the specific opiate antagonist naloxone is able to decrease the self-stimulating behaviour elicited by electrical stimulation of certain brain sites (Belluzzi and Stein, 1977; Stein and Belluzzi, 1978). This may be evidence that endorphin systems are involved in brain stimulation reward.

Hypothalamic-pituitary hormones may function as precursor molecules for so-called neuropeptides which may be generated by enzymatic cleavage (De Wied, 1969; De Wied, Van Wimersma Greidanus and Bohus, 1974). Neuropeptides related to ACTH/MSH/β-LPH and those related to the neurohypophyseal hormones are implicated in the formation and maintenance of new behaviour patterns. It has been postulated that neurohypophyseal hormones (i.e. vasopressin and oxytocin) and their fragments modulate brain processes selectively to consolidate, retrieve and repress recently acquired information (De Wied, 1977; van Ree, Bohus, Versteeg and De Wied, 1978b). Since learning and memory processes play an important role in the mechanism by which drug injection gains and maintains control over behaviour, experiments were performed on the influence of these neuropeptides on the acquisition of self-administering behaviour. It was shown that des-glycinamide[9], arginine[8], vasopressin (DG-AVP) reduced the acquisition of heroin self-administration in a dose-dependent manner (van Ree and De Wied, 1977a). The inhibitory effect was hardly present in the first phase of testing, but decreased gradually thereafter. A similar attenuation of the behaviour was observed when DG-AVP was given in the first phase of testing only, indicating that the effect of DG-AVP was long lasting. The effect of DG-AVP in heroin self-administration is due to a central effect, since a much lower amount of DG-AVP was required when the peptide was administered intracerebroventricularly (van Ree and De Wied, 1977b). The physiological involvement of vasopressin in the acquisition of heroin self-administration was suggested by the finding that intracerebroventricularly applied specific vasopressin anti-serum markedly stimulated heroin self-administration (van Ree and De Wied, 1977b). According to structure activity studies the covalent ring-structure of vasopressin appears to be as important for attenuating heroin self-administration as it is for the enhancement of memory consolidation (De Wied, 1976b, van Ree *et al.*, 1978b). Assuming that vasopressin acts similarly in heroin self-administration and memory consolidation it can be expected that this neuropeptide is only effective during the development of the behaviour or when the behaviour is changed in response to variations of the reinforcement or environmental cues. Vasopressin might be less effective once the behaviour of the animals is under the stringent control of the reinforcer or the reinforcement schedules. Indeed, it has been shown that under such conditions, DG-AVP did not affect morphine self-administration in mon-

keys (Mello and Mendelson, 1979). The degree of reinforcement control over behaviour may thus be of importance with respect to the effectiveness of DG-AVP. This possibility is supported by data on self-stimulating behaviour elicited from electrodes implanted in the ventral-tegmental-medial-substantia nigra area which contains the cell bodies of the mesolimbic and mesocortical dopaminergic pathways (Dorsa and van Ree, 1979). Self-stimulating behaviour was decreased by DG-AVP at current intensities near the threshold for eliciting this behaviour but had no effect at current intensities which evoked maximal response rates. An opposite effect was observed with the C-terminal tripeptide of oxytocin (PLG), which had previously been shown to increase heroin self-administration. The striking similarity of the effects of these peptides on electrical self-stimulating and heroin self-administration could suggest that these peptides influence heroin self-administration by interfering with transmission in nigrostriatal or more likely in mesolimbic dopaminergic pathways. This is consistent with the assumption that dopaminergic systems in the brain are critically involved in brain reward.

The data reviewed here suggest that the reward mechanisms triggered by heroin and involved in the acquisition and maintenance of drug seeking behaviour are under the control of neurohypophyseal hormones and their fragments. These neuropeptides may thus contribute to the initiation of drug-seeking behaviour. Neuropeptides from other pituitary hormones may be also involved in the complex interaction of addictive drugs with brain homeostatic mechanisms. For example, it was shown that $ACTH_{4-10}$ which has been implicated in such brain processes as motivation and attention (De Wied, 1976a) interfered selectively with the discriminative internal stimuli elicited by narcotic injections (Colpaert, Niemegeers, Janssen, van Ree and De Wied, 1978). The pituitary-brain neuropeptide systems may contribute to the adaptation of the individual to the environment. A disturbance in one or more of these systems may lead to a state in which drug-seeking behaviour can reliably be expected to develop.

REFERENCES

Belluzzi, J. D. and Stein, L. (1977). Enkephalin may mediate euphoria and drive-reduction reward. *Nature* **266:** 556–558.

Brady, J. V. and Griffiths, R. R. (1976). Behavioral procedures for evaluating the relative abuse potential of CNS drugs in primates. *Fedn Proc. Fedn Am. Socs exp. Biol.* **35:** 2245–2253.

Cadell, T. E. and Cressman, R. J. (1972). Group social tension as a determinant of alcohol consumption in Macaca mulatta. In: *Medical Primatology—Part II* (Goldsmith, E. I. and Moor-Jankowski, J., Eds), pp. 250–259. Karger, Basel.

Carnathan, G., Meyer, R. E. and Cochin, J. (1977). Narcotic blockade, length of addiction, and persistence of intravenous morphine self-administration in rats. *Psychopharmacology* **54:** 67–71.

Colpaert, F. C. (1977). Narcotic cue and narcotic state. *Life Sci.* **20:** 1097–1108.

Colpaert, F. C. (1978). Discriminative stimulus properties of narcotic analgesic drugs. *Pharmac. Biochem. Behav.* **9:** 863–887.

Colpaert, F. C., Niemegeers, C. J. E., Janssen, P. A. J., van Ree, J. M. and De Wied, D. (1978). Selective interference of $ACTH_{4-10}$ with discriminative responding based on the narcotic cue. *Psychoneuroendocrinology* **3:** 203–210.

Deneau, G., Yanagita, T. and Seevers, M. H. (1969). Self-administration of psychoactive substances by the monkey. *Psychopharmacologia* **16:** 30–48.

De Wied, D. (1969). Effects of peptide hormones on behavior. In: *Frontiers in Neuroendocrinology* (Ganong, W. F. and Martini, L., Eds.), pp. 97–140. Oxford University Press, New York.

De Wied, D. (1976a). Hormonal influences on motivation, learning and memory processes. *Hosp. Pract.* **11:** 123–131.

De Wied, D. (1976b). Behavioral effects of intraventricularly administered vasopressin and vasopressin fragments. *Life Sci.* **19:** 685–690.

De Wied, D. (1977). Peptides and behavior. *Life Sci.* **20:** 195–204.

De Wied, D., Van Wimersma Greidanus, Tj. B. and Bohus, B. (1974). Pituitary peptides and behavior: influence on motivational, learning and memory processes. In: *Neuropsychopharmacology*, Excerpta Medica International Congress Series No. 359, pp. 653–658, Excerpta Medica, Amsterdam.

Dorsa, D. M. and van Ree, J. M. (1979). Modulation of substantia nigra self-stimulation by neuropeptides related to neurohypophyseal hormones. *Brain Res.* In press.

Esposito, R. and Kornetsky, C. (1977). Morphine lowering of self-stimulation thresholds: Lack of tolerance with long-term administration. *Science* **195:** 189–191.

Fraser, H. F., Van Horn, G. D., Martin, W. R., Wolbach, A. B. and Isbell, H. (1961). Methods for evaluating addiction liability. (A) "Attitude" of opiate addicts toward opiate-like drugs. (B) a short-term "direct" addiction test. *J. Pharmac. exp. Ther.* **133:** 371–387.

Goldberg, S. R. and Tang, A. H. (1977). Behavior maintained under second-order schedules of intravenous morphine injection in squirrel and rhesus monkeys. *Psychopharmacology* **51:** 235–242.

Griffiths, R. R. and Bigelow, G. E. (1978). Commonalities in human and infrahuman drug self-administration. In: *The Bases of Addiction* (Fishman, J., Ed.), pp. 157–174. Dahlem Konferenzen 1978, Berlin.

Harrigan, S. E. and Downs, D. A. (1978). Self-administration of heroin, acetylmethadol, morphine and methadone in rhesus monkeys. *Life Sci.* **22:** 619–624.

Headlee, C. P., Coppock, H. W. and Nichols, J. R. (1955). Apparatus and technique involved in a laboratory method of detecting the addictiveness of drugs. *J. Am. Pharm. Ass.* **44:** 229–231.

Hökfelt, T., Elde, R., Johansson, O., Terenius, L., and Stein, L. (1977). The distribution of enkephalin-immunoreactive cell bodies in the rat central nervous system. *Neurosci. Lett.* **5:** 25–31.

Hoffmeister, F. (1979). Progressive-ratio performance in the rhesus monkey maintained by opiate infusions. *Psychopharmacology* **62:** 181–186.

Kalant, H. (1978). Behavioral criteria for tolerance and physical dependence. In: *The Bases of Addiction* (Fishman, J., Ed.), pp. 199–220. Dahlem Konferenzen 1978, Berlin.

Kalant, H., Engel, J. A., Goldberg, L., Griffiths, R. R., Jaffe, J. H., Krasnegor, N. A., Mello, N. K., Mendelsohn, J. H., Thompson, T. and van Ree, J. M. (1978). Behavioral aspects of addiction—Group Report. In: *The Bases of*

Addiction (Fishman, J., Ed.), pp. 463–496. Dahlem Konferenzen 1978, Berlin.

Kelleher, R. T. and Goldberg, S. R. (1975). General introduction: Control of drug-taking behavior by schedules of reinforcement. *Pharmac. Rev.* **27:** 291–299.

Maroli, A. N., Tsang, W. K. and Stutz, R. M. (1978). Morphine and self-stimulation: Evidence for action on a common neural substrate. *Pharmac. Biochem. Behav.* **8:** 119–123.

Mello, N. K. and Mendelson, J. H. (1978). Behavioral pharmacology of human alcohol, heroin and marihuana use. In: *The Bases of Addiction* (Fishman, J., Ed.), pp. 133–158. Dahlem Konferenzen 1978, Berlin.

Mello, N. K. and Mendelson, J. H. (1979). Effects of the neuropeptide DG-AVP on morphine and food self-administration by dependent rhesus monkey. In press.

van Ree, J. M. and De Wied, D. (1977a). Modulation of heroin self-administration by neurohypophyseal principles. *Eur. J. Pharmac.* **43:** 199–202.

van Ree, J. M. and De Wied, D. (1977b). Heroin self-administration is under control of vasopressin. *Life Sci.* **21:** 315–320.

van Ree, J. M., Slangen, J. L. and De Wied, D. (1974). Self-administration of narcotic drugs in rats: dose-response studies. In: *Neuropsychopharmacology*, Excerpta Medica International Congress Series no. 359, pp. 231–239. Excerpta Medica, Amsterdam.

van Ree, J. M., Slangen, J. L. and De Wied, D. (1978a). Intravenous self-administration of drugs in rats. *J. Pharmac. exp. Ther.* **204:** 547–557.

van Ree, J. M., Bohus, B., Versteeg, D. H. G. and De Wied, D. (1978b). Neurohypophyseal principles and memory processes. *Biochem. Pharmac.* **27:** 1793–1800.

van Ree, J. M., Dorsa, D. M. and Colpaert, F. C. (1978c). Neuropeptides and drug dependence. In: *Characteristics and Function of Opiods* (van Ree, J. M. and Terenius, L., Eds.), pp. 1–12. Elsevier/North-Holland Biomedical Press, Amsterdam.

van Ree, J. M., Smyth, D. G. and Colpaert, F. C. (1979). Dependence creating properties of lipotropin C-fragment (β-endorphin): evidence for its internal control of behavior. *Life Sci.* **24:** 495–502.

Schuster, C. R. and Thompson, T. (1969). Self-administration of and behavioral dependence on drugs. *A. Rev. Pharmac.* **9:** 483–502.

Skinner, B. F. (1938). *The Behavior of Organisms*. Appleton-Century-Crofts, New York.

Spealman, R. D. and Goldberg, S. R. (1978). Drug-self-administration by laboratory animals: Control by schedules of reinforcement. *A. Rev. pharmac. tox.* **18:** 313–339.

Spragg, S. D. S. (1940). Morphine addiction in chimpanzees. *Comp. Psychol. Monogr.* **15:** 79–132. Johns Hopkins Press, Baltimore.

Stein, L. and Belluzzi, J. D. (1978). Brain endorphins and the sense of well-being: A psychobiological hypothesis. In: *The Endorphins* (Costa, E. and Trabucchi, M., Eds.). Advances in Biochemical Psychopharmacology, Vol. 18, pp. 299–311, Raven Press, New York.

Thompson, T. and Pickens, R. (1969). Drug self-administration and conditioning. In: *Scientific Basis of Drug Dependence* (Steinberg, H., Ed.), pp. 177–198, J. & A. Churchill, London.

Thompson, T. and Pickens, R. (1975). An experimental analysis of behavioral factors in drug dependence. *Fedn Proc. Fedn Am. Socs exp. Biol.* **34:** 1759–1770.

Thompson, T. and Unna, K. R. (Eds.) (1977). *Prediction of Abuse Liability of Stimulant and Depressant Drugs*. National Academy of Sciences National Research Council, Washington D.C.

Thompson, T. and Young, A. M. (1978) Relevance of animal models for human addiction. In: *The Bases of Addiction* (Fishman, J., Ed.), pp. 119–132. Dahlem Konferenzen 1978, Berlin.

Watson, S. J., Akil, H., Berger, Ph. A. and Barchas, J. D. (1979). Some observations on the opiate peptides and schizophrenia. *Archs gen. Psychol.* **36:** 35–41.

Weeks, J. (1962). Experimental morphine addiction: method for automatic intravenous injection in unrestrained rats. *Science* **138:** 143–144.

Weeks, J. R. (1975). Environmental influences affecting the voluntary intake of drugs: an overview. *Fedn Proc. Fedn Am. Socs exp. Biol.* **34:** 1755–1758.

Weeks, J. R. and Collins, R. J. (1964). Factors affecting voluntary morphine intake in self-maintained addicted rats. *Psychopharmacologia* **6:** 267–279.

Weeks, J. R. and Collins, R. J. (1968). Patterns of intravenous self-injection by morphine-addicted rats. *Res. Publs Ass. nerv. ment. Dis.* **46:** 288–298.

Wilson, M. C., Hitomi, M. and Schuster, C. R. (1971): Psychomotor stimulant self-administration as a function of dosage per injection in the rhesus monkey. *Psychopharmacologia* **22:** 271–281.

Wise, R. A. (1978). Catecholamine theories of reward: a critical review. *Brain Res.* **152:** 215–247.

Woods, J. H. and Schuster, C. R. (1971). Opiates as reinforcing stimuli. In: *Stimulus Properties of Drugs* (Thompson, T. and Pickens, R., Eds), pp. 162–175. Appleton-Century-Crofts, New York.

Yokel, R. A. and Pickens, R. (1973). Self-administration of optical isomers of amphetamine and methyl-amphetamine by rats. *J. Pharmac. exp. Ther.* **187:** 27–33.