ACTA NEUROBIOL. EXP. 1980, 40: 665-686

THE PHARMACOLOGY OF CATECHOLAMINE INVOLVEMENT IN THE NEURAL MECHANISMS OF REWARD

A. WAUQUIER

Department of Pharmacology, Janssen Pharmaceutica
Beerse, Belgium

Abstract. The neurophysiological basis of motivation became a major research goal with the discovery of brain self-stimulation. Correlative anatomical and neurochemical mapping of self-stimulation sites led to the catecholamine theory of self-stimulation. The present review summarizes the pharmacological evidence pertinent to this theory and formulates conclusions on the functional role of catecholamine systems in behavior reinforced by electrical brain-stimulation.

INTRODUCTION

> "Subjects *learn* to do things, *if* they are rewarded for doing them *and if* they are motivated to do them" (Olds, 44).

Reward is a central concept in the study of behavior. Motivation or drive which results in reward manifests itself through approach behavior. Behavior is steered by reward: the general term reinforcer refers to the fact that it increases the probability of the responses preceding and leading to reward. Reinforcement refers to the process through which reward steers the behavior. Depending on the theoretical context, reward results from drive-reduction (25), is a confirming reaction (65), acts as an incentive (57) or is a drive-inducer (55).

The discovery by Olds and Milner (43) that rats rapidly learn to press a lever which triggers electrical brain-stimulation through a chronically implanted electrode, suggested that the brain areas concerned with reward had been detected. In contrast to the concept that reward is a property of certain unidentified systems, these experiments also suggested that there are reward or drive neurons (42). Activation of these neurons not only provides strong reinforcement, but serves drive-reduction, drive-induction or incentive motivation. The specific standpoint taken, depends on the theoretical framework in which the experiments are interpreted. Some experiments suggest that self-stimulation simulates consummatory responses to natural drives, whilst others suggest that the stimulation-produced incentives are concurrent with natural drives. There is an overlap between areas sustaining self-stimulation and basic drives, but there is not necessarily a causal relationship between them. The self-stimulation "system" is rather superimposed on specific drives, which, however, act as gates and co-determine behavior.

The control of behaviour does not only depend on interoceptive stimuli (physiological or cognitive), but also on exteroceptive and proprioceptive stimuli. On the input side, there are processes which are responsible for the initiation of behavior. On the output side, there is the behaviour itself. On the basis of the behavioral analysis, inferences are made concerning the function of the brain, and the role of drives. One concept holds that self-stimulation does not need to rely on a drive substrate, but that the stimulation finally produces response facilitation (35). The self-stimulation substrate involves neurons which constitute, or are connected to, a "final common pathway", interacting with ongoing behavior. Many experiments suggest that catecholamine neurons are critical parts of this final common pathway (15, 21, 35–37, 75, 78).

The present review mainly emphasizes the pharmacological evidences related to the catecholamine hypothesis of self-stimulation, taking various determinants of behavior into account. It further considers the functional aspects of brain-structures sustaining self-stimulation as related to the control of behavior.

BRAIN SELF-STIMULATION PATHWAYS

Through the discovery and experiments on self-stimulation behavior, the neurophysiological bases of motivation became a major research goal. Original mapping studies suggested that the medial forebrain bundle (MFB) was the anatomical substrate of intracranial self-stimulation (ICS). Neurochemical mapping studies and correlative anatomical studies on ICS sustaining sites switched the emphasis to the noradrenaline (NA) and dopamine (DA) pathways, which originated the "catecholamine hypothesis" of ICS. Recent studies further speculate on the role of enkephalins and other neuropeptides in ICS.

MFB: original anatomical substrate. Mapping studies (44) suggested that sites sustaining self-stimulation were arranged along the bidirectional fiber system the medial forebrain bundle (MFB). As self-stimulation rate increased the nearer the electrodes were implanted to the lateral hypothalamus, it was postulated that this structure was a focus. Lesions of the MFB in most cases only temporarily suppressed self-stimulation (33), suggesting that the system was rather diffusely organized. In addition, the lesion studies suggested a functional redundancy and plasticity in the organization of brain reward (68). The lesion studies, however, also showed that different forms of reward take place in different structures (41).

Though the original suggestion that the MFB is the anatomical substrate of ICS was able to cover most of the data, it remained speculative, mainly because of the highly complex and ill-defined conglomeration of neurons constituting the MFB (34). In addition, different sites, which are not part of the MFB, were found to sustain ICS (e.g. substantia nigra, caudate nucleus, raphe nuclei) including structures at the pontine level (see further).

Neurochemical brain mapping. Histochemical mapping, through the Falck-Hillarp technique, revealed the presence in the brain of NA, DA and 5-hydroxytryptamine (5-HT) neurons (1, 17). The ascending NA and DA systems were later depicted by Ungerstedt (67), and detailed by Lindvall and Björklund (31).

The NA fibres originate from nuclei in the midpontine region forming two bundles (ventral and dorsal) at the mesencephalic level. The dorsal NA bundle, originating in the locus coeruleus (A_6, nomenclature of Dahlström and Fuxe 17), fans out innervating practically all cortical (neocortical and cerebellar) areas; the ventral NA bundle, originating from nuclei in the caudal brain stem, innervate various hypothalamic nuclei. The DA fibers originate in ventral midbrain (substantia nigra, dorsal to the interpeduncular nucleus) innervate the caudate nucleus (nigrostriatal pathway) and limbic structures such as the nucleus accumbens (mesolimbic pathway). In addition, Thierry et al. (63, 64) and Lindvall et al. (32) described the existence of a "mesocortical DA pathway" also originating in ventral midbrain and innervating cortical areas, especially the limbic and basal parts of the frontal cortex. Thus, all these neurons are ascending systems and they coalesce at cerebral and cerebellar cortex, basal ganglia and limbic structures.

The catecholamine hypothesis. The finding that self-stimulation was enhanced by amphetamine, an effect thought to be due to a release of noradrenaline (NA) (58) and that self-stimulation was found in cell bodies of the ventral midbrain (19) which also released catecholamines (CA), together with the coincidence of self-stimulation sites with the mapped CA systems, originated the CA hypothesis of self-stimulation (12–14). The high ICS in MFB at the lateral hypothalamic level could be due to an activation of the CA fibers running through this site.

The CA hypothesis predicted that self-stimulation would be found in the whole DA and NA systems, i.e. cell bodies, pathways and terminal structures. This hypothesis was confirmed for the dorsal NA system, for the nigro-striatal and mesolimbic DA system (6, 13, 15, 50, 60) and evidence accumulated for the DA mesocortical system (e.g. 38).

The evidence for the involvement of these systems is based on: anatomical sites sustaining self-stimulation, including the critical tests that ICS is also found at the cell body level (16); lesioning studies, implicating also the effects of the neurotoxin 6-hydroxydopamine, specifically aimed at destroying DA pathways; release of transmitters during self-stimulation; and pharmacological experiments.

A critical question remains regarding the functional role of these CA pathways, since most studies only implicate their involvement, which though necessary, is not sufficient. Further, ICS is also found in non-CA structures, but the possibility of indirect activation of CA's is not excluded. Their wide-spread distribution does not suggest a single specific function. Mainly based on pharmacological experiments, it appears that CA systems, and more specifically DA systems are important links in the control of behavior. DA pathways feed into structures having a direct function in motor control. *Motivation* could be conceived as "the system that controls what gets into and through the motor system" (35) (sustained by DA pathways). Reinforcement could be sustained by structures (NA pathways) having a *memory-consolidation* function.

PHARMACOLOGICAL EXPERIMENTS IN RATS

Different relatively complete reviews on the pharmacology of self-stimulation have been written in the past (e.g. 73). Herein, particular groups of drugs and experiments relevant to the catecholamine hypothesis and theoretical aspects of self-stimulation are described.

Any interpretation of changes in lever-pressing for brain-stimulation in terms of reward effects, is confounded by the fact that many variables can affect performance (89). A much cited experiment in this respect is that of Roll (48): she showed that rats inhibited by treatment with a NA synthesis inhibitor, self-stimulated normally when these rats were aroused and placed on the lever. Thus, the inhibition appeared not to be due to a specific reward effect, but to a performance deficit. In general, the validity of conclusions based on pharmacological experiments, heavily depend on the methodology applied and the extent of the extrapolations based on specific behavioral tests and paradigms.

Activation by stimulants. Central stimulants such as apomorphine, amphetamine and cocaine enhance self-stimulation, especially when the control self-stimulation level is low and some (apomorphine, amphetamine) depress high rates of self-stimulation at relatively high dose-levels. There are a number of studies indicating that their action is related to activating DA-systems (see in 82–84). The facilitation is independent of the specific operant used, the experimental paradigm and occurs with both appetitive and aversive behavior (40, 75).

Non-physiological activation of a system sustaining ICS is disrupting. In fact, at high doses of stimulants depression is observed which coincides with the time course of the induced stereotypy. The depression is most pronounced with apomorphine, whereas s.c. doses of cocaine, not producing stereotypy, do not depress ICS. It is reasonable to assume that stereotyped behavior, which is characterized by a reduction of the behavioral pattern into fragments occurring at a high frequency, is competing with adaptive behavior. Therefore, ICS is depressed though not completely eliminated.

At moderate or relatively high dose-levels of stimulants, response enhancement is observed provided base-line rates of ICS are not high. In addition, there is a delay of extinction, that is, rats continue to press the lever even when brain-stimulation is no longer available. Clearly, the lever-pressing rate is at the same level as that seen during reinforcing stimulation. The response enhancement has been ascribed to the rewarding properties of the drugs, as evidenced in the self-administration experiments and because of their abuse liability (except for apomorphine).

It was argued by Crow (15) that a drug activating a reward system would tend to depress rather than enhance self-stimulation. He further argued that stimulants might cause response enhancement if it can be shown that they enhance the release of neurotransmitters via neural activity. Tyramine, a drug causing a non-impulse dependent release of CA, indeed suppressed self-stimulation (22).

Wise (96) argued that amphetamine and rewarding stimulation might enhance each other's rewarding action. The response increase would result, for instance, from recruitment of amine systems not directly activated through a localized stimulation.

CNS stimulants might also cause response perseveration, independently of their possible threshold reduction effects. The response enhancement at low control rates of self-stimulation appears equal to the enhanced performance during extinction (no reinforcer available), and also occurs in non-self-stimulating rats which have had experience with lever-pressing (unpublished observations). This suggests that direct locomotor facilitation might also be involved in the enhanced ICS.

A number of DA-agonists behave differently, in that they lack the motor facilitating properties, and do not enhance self-stimulation (76). Intracranial injections of these compounds, suggest that the differential effects are due to their preferential action in either striatum or accumbens (9–11). This structural difference, however, does not completely explain the differential action which might indicate that one has to take the involvement of different DA receptors into account (8).

The compounds which enhance self-stimulation are those also which induce locomotor activity, agitation and sniffing, which suggest that they enhance self-stimulation by facilitating approach to the environment. In terms of the Valenstein's (69) hypothesis, these drugs have rewarding properties by facilitating interaction with the environment.

Impairment by neuroleptics. A variety of neuroleptics belonging to various chemical classes and with a widely different pharmacological profile, were tested on brain self-stimulation (see survey in 73, 75). In spite of the large differences among the neuroleptics, they all inhibited self-stimulation in a dose-dependent way. This was observed in a variety of experimental paradigms and with different electrode locations (e.g. 19, 46, 49, 81). These findings suggest that neuroleptics elicit their effects through an action on a common substrate involved in operant behavior. There appeared, however, to be considerable differences with respect to potency (73, 75, 81, 85–88). The inhibition of self-stimulation is inversely related to the baseline rates of responding induced by different stimulus parameter combinations, which indicates that inhibition is more difficult to obtain when the activity (or reinforcement) level is high.

Neuroleptics differ in their relative potency in blocking the stereotypy induced by apomorphine (indicating DA-activity), in blocking the norepinephrine toxicity (indicating NA-activity) and in blocking the bilateral forepaw convulsions induced by tryptamine (indicating serotonergic activity) (28, 40). In addition, some neuroleptics possess inherent anticholinergic activity or are histamine blockers.

The inhibition of ICS is significantly correlated with tests suggesting DA- and 5 HT-blockade (r_s respectively 0.947 and 0.650, $P < 0.01$). Correlations might only indicate potency relationships, but spectral mapping analysis applied to the same data demonstrated a close relation between the inhibition of ICS and tests sensitive to dopamine (75).

The fact that relatively high doses of specific neuroleptics cause catalepsy in animals and extrapyramidal symptoms in humans, suggested that motor incapacitation is related to the suppressing effects of neuroleptics on self-stimulation. In fact, there is a significant correlation between the ED_{50} values of catalepsy and self-stimulation inhibition ($r_s = 0.736$, $P < 0.01$) (73).

Though subtle motor effects can be involved, catalepsy is only seen at doses higher than those inhibiting ICS. Different tests have been designed to demonstrate that the inhibition of ICS by neuroleptics is a specific effect on reinforcement (see e.g. survey in 96). For example, neuroleptic-treated rats tend to self-stimulate at normal rates during the first minutes of a session and then responding gradually decreased, following an extinction pattern. This suggests that the cues associated with self-stimulation are not affected and further that the rats are still able to emit the appropriate response. An alternative interpretation of the same experiment is, that neuroleptic-treated rats are unable to maintain responding. Because neuroleptics appear to interfere with any operant behaviour requiring complex motor activity, it is appropriate to study their effects using different paradigms and to alter the response required to obtain brain-stimulation.

We studied (unpublished observations) the effects of spiperone on ICS in a situation where the lever was positioned high or low, and where a strong pressure (60 g) or a light pressure (10 g) was required. In all cases, there were no differences in the inhibitory effects of spiperone, suggesting that increasing the task difficulty did not alter the sensitivity to a neuroleptic, provided lever-pressing remained the required response.

In another study (88), we compared the effects of 4 different neuroleptics on licking a dry drinknipple and lever-pressing for self-stimulation. Licking appeared more sensitive to the inhibiting properties of these neuroleptics. The differential sensitivity was not due to baseline differences (strength of reinforcement), schedule differences or the motor activity involved in both responses, but rather to different thresholds of reinforcement of lever-pressing and licking.

Such experiments suggest that reinforcement pathways differ and depend on the required response. This might imply the existence of different reward mechanisms which are response-specific, as suggested by White (94).

Interaction studies. In between the input to the caudate nucleus by the nigrostriatal DA system, which at its origin in the substantia nigra itself is regulated by other transmitter systems, and its output to the motor effector systems, highly complicated interactions of various transmitters exist. On the basis of the proposed interaction between the DA neurons and the cholinergic interneurons in the caudate, one expects a mutual antagonism between neuroleptics and anticholinergics. Earlier behavioral studies showed that catalepsy and inhibition of avoidance induced by neuroleptics could be antagonized by anticholinergics; in biochemical experiments, it was shown that the increase in homovanillic acid after neuroleptic treatment (a measure of enhanced DA turnover) could be reduced by anticholinergics (see references and literature survey in 92).

It was established that anticholinergics (e.g. dexetimide) or antiparkinsonian agents (e.g. benztropine, trihexyphenidyl) in a dose-related fashion antagonized the inhibition of self-stimulation induced by neuroleptics (75, 85, 90–92). Further studies (75, 87) showed that the inhibition obtained with neuroleptics at the same dose-levels sufficient to block DA, NA and eventually 5 HT receptors were not antagonized by these agents. It was postulated that one of the requirements of the antagonist was that they should enhance the respective transmitters at their receptor site. The results of such a study confirmed our hypothesis (75, 87).

A normalization of the input to the caudate restores behavior, which gives pharmacological evidence that the DA nigrostriatal system must function within a certain range in order for normal behavior to occur. Conversely, it was reasonable to expect that the effects on self-stimulation produced by apomorphine could be potentiated or antagonized. In order to differentiate between the putative transmitters involved, rats were treated with different doses of apomorphine and pretreated with either phenoxybenzamine (NAα-blocker), propranolol (NAβ-blocker), pimozide (DA-blocker), pizotifen (5 HT-blocker), dexetimide (muscarinic ACh blocker) or picrotoxin (GABA-blocker) (74). When the control baseline self-stimulation rate was high, all compounds decreased self-stimulation. When the control baseline self-stimulation rate was low, all compounds except pimozide, enhanced self-stimulation.

Compared with the effects of apomorphine alone phenoxybenzamine, pimozide and pizotifen decreased and propranolol, dexetimide and picrotoxin increased the response facilitation produced by apomorphine. Essentially similar results were obtained with another DA agonist piribedil. Such experiments allow speculations to be made on the "sign" of the interaction between differently mediated neurons, resulting in behavioral potentiation or conversely, antagonism of DA activation. These pharmacological experiments, of course, do not indicate where these neuronal interactions occur. Attempts to localize interactions make use of intracranial injection techniques. One of these experiments concerns an attempt to reverse the neuroleptic-produced inhibition of self-stimulation by intracranial injections of other drugs, such as anticholinergics in the caudate nucleus or the nucleus accumbens. Injections of scopolamine or dexetimide in the caudate nucleus did not reverse the inhibition produced by pimozide or spiperone (62), but the anticholinergics partially reversed the inhibition when injected into the nucleus accumbens. Because the caudate nucleus is a large structure and intracranial injection spreads only 1 mm, it might not be surprising that no reversal was found, especially also in view of the intracaudate functional differences (7). It might be that the antagonism of neuroleptics occurs at the level of the substantia nigra: it is postulated that "autaptic" DA receptors are located there; there is also a topographic projection from the nigra region to the caudate and the accumbens; cholinergic neurons might synapse at the level of the nigra (5). Preliminary experiments did show that anticholinergics partially reversed the neuroleptic-induced inhibition, when injected in the nigra.

These partial effects might be due to the fact that the neuroleptics block DA receptors at different brain sites and only a "concerted action" of the antagonist at these different sites produces a complete reversal of the neuroleptic-induced inhibition.

Again, all these studies suggest that a functionally intact DA system is required for normal behavior.

Conclusions. Operant behavior is specifically inhibited by neuroleptics; this inhibition cannot be interpreted purely in terms of a motor deficit, but is better understood if it is postulated that neuroleptics interfere at the level of the basal ganglia, structures subserving a sensorimotor integrative function. Neuroleptics which interfere with DA systems will, at different dose levels and dependent on their relative specificity, produce a lack of sustained self-stimulation.

Central stimulants enhance operant behavior also by an action at the level of the basal ganglia. This effect cannot be explained by increased reinforcement but is partly due to increasing interaction with the environment in which the learned responses have the highest probability of occurrence.

Drug interaction studies demonstrated functional interactions at the level of basal ganglia in either restoring behavior or in potentiating response facilitation. Intracranial injection studies only partially elucidate sites of action.

Different dopaminergic systems feed into cortical and basal ganglia structures which are concerned with sensory transformation, motor initiation and control of motor behavior (21, 35, 36). Their activation leads to a disinhibition of programmed neural circuits (47) resulting in repetition and maintenance of behavior. Self-stimulation is assumed to be partly due to an activation of pathways which feed into structures having a motor control function.

PHARMACOLOGICAL EXPERIMENTS IN DOGS

For obvious reasons, rats were the subjects of choice for the pharmacological self-stimulation experiments. Drug-results obtained in one species may not be generalized to other species. There are few reports of drug-effects on self-stimulation in other species. Stark (58) tested cholinergics, anticholinergics, serotonin-like and serotonin-antagonistic drugs in dogs. Horovitz et al. (24) studied the effects of chlorpromazine in cats. They reported that chlorpromazine decreased self-stimulation in the lateral hypothalamus and equally in the caudate nucleus. In 2 out of 7 cats, 0.5 and 1.0 mg/kg of chlorpromazine did not affect responding. Our studies (72, 75, 77, 79, 80) dealt with the effects of neuroleptics, CNS stimulants and the interactions of both in dogs. Two different paradigms were used.

Free situation. Dogs (beagles and labradors) were implanted with bipolar electrodes in different brain regions. After the initial shaping, dogs were further trained to press a lever for brain-stimulation during x times 10 periods (x being the number of positive electrodes).

Self-stimulation was supported by 23 out of 26 electrodes in the nucleus accumbens, 15 out of 24 in the lateral preoptic region, 5 out of 8 in the amygdala region, 4 out of 9 in the lateral hypothalamus and 4 out of 9 in the substantia nigra region. Electrodes producing unstable response rates were, however, not used for drug testing. Electrodes in the anterior forebrain regions (nucleus accumbens, lateral preoptic area and basolateral amygdala) sustained self-stimulation slowly and mostly in bouts; delayed extinction was also apparent. This contrasted strongly with stimulation in the lateral hypothalamus or substantia nigra, which was characterized by continuous fast lever-pressing and instantaneous extinction.

After at least 6 sessions (3 sessions a week) the dogs were treated s.c. with either pimozide, haloperidol, fluanisone, pipamperone or azaperone.

There were no clearcut site-related effects and self-stimulation in most sites was dose-relatedly inhibited. Atypical dose-response curves were obtained with specific dopaminergic blocking neuroleptics (pimozide, haloperidol, fluanisone) apparently because of motor effects. Neuroleptics (pipamperone, azaperone) which preferentially block noradrenergic and serotonergic receptors appeared to be potent inhibitors of self-stimulation. The fact that these neuroleptics also block self-stimulation in sites where dopamine might play an important role might confirm the concepts of Franklin et al. (20) that dopaminergic self-stimulation also requires a transsynaptic activation of noradrenergic structures.

External stimulus control of ICS. Dogs can easily be conditioned to press a lever for brain stimulation only following the onset of a tone of 1,000 Hz (discriminative stimulus or S^D) (77, 79). During the absence of the tone ($S^{\triangle}$) lever-pressings were never reinforced (Paradigm based on Pavlova et al. 45). In a similar way to the Lenzer and Frommer experiments (30) most responding during $S^{\triangle}$ occurred immediately following S^D termination. An arbitrarily chosen 5 s period following termination of S^D was considered as "overshoot" (post-reinforcement).

The acquisition of this discrimination in dogs, which had previously learned to press a lever for brain stimulation, is fairly rapid. Once learned for one electrode site transfer to other positive electrods was established during one session of 20 trials. Stability in latency and responding following the acquisition phase was reached after 6–9 sessions, that is short latencies between the onset of S^D and the first response, stable lever-pressing and few to no intertrial responses. The amount of lever-pressing during S^D is highly stable but differs between electrodes and dogs. With some electrodes, responding during $S^{\triangle}$ occurred, however, this was far below responding during S^D. These intertrial responses were also stable and apparently determined by the specific brain region stimulated.

These experiments demonstrate that ICS can be brought under external S control. Thus S^D becomes a secondary drive stimulus or acquires incentive motivational properties (66) through classical conditioning.

Haloperidol-apomorphine interaction. In forebrain ablated animals (26) it appeared that self-stimulation could still be found, provided descending pathways were intact and simple operants were used. The responses, however, lacked cortical (?) control, so that extinction could not be observed (continuation of the performance in the absence of reinforcing brain-stimulation).

This experiment points to the important role of forebrain structures in differentiating between relevant and non-relevant responses. The disturbance of both external and internal S control of behavior and its restoration by a DA blocker was studied (79).

Using the paradigm in the dog described, in which ICS is controlled by an external S, dogs were treated with apomorphine, haloperidol and combinations of both drugs.

Apomorphine disrupted the behavior, its effects were multifold and related to the dose. At relatively low doses apomorphine produced a loss of external S control, since the dogs also performed during S^{Δ}. Higher doses also caused a loss of the reinforcing S control by producing erratic responding throughout S^{D} and S^{Δ}. Finally, higher doses disturbed the performance through its stereotypogenic effect.

In this situation haloperidol was found to restore both external and internal S control. These effects again are multifold and dose-dependent. Low doses of haloperidol either restored performance capability by reducing stereotypy to a mild stereotypogenic lever-pressing, or potentiated intermediate doses of apomorphine by increasing stereotypy. Intermediate doses of haloperidol restored the external S control and the capability of the electrical stimulation to reinforce behavior. High doses again disrupted performance because of the inherent response depressant effects of haloperidol, though stereotypy was completely antagonized.

Thus over-stimulation of DA pathways disturbs both internal and external stimulus control of behavior. In short, the animals were no longer able to perceive or respond to both external and internal cues. The fact that neuroleptics are able to restore normality in such animals is of relevance to psychotic diseases such as schizophrenia, which may involve a dysfunction of feedback processes, rather than a behavioral disturbance.

Visceral feedback control. Experiments by Ward and Hester (70) suggested that visceral feedback was not essential for self-stimulation, since vagotomy, sympathectomy and sectioning of the pelvic splanchnic nerves did not affect ICS in cats. However, other observations suggest that the phenomenon of ICS is modulated by feedback from the periphery (see survey in 52).

Ball (4) observed that subdiaphragmal vagotomy did not change the number of lever-pressings for ICS, but significantly elevated the threshold. Sadowski et al. (53) described hyperthermia produced by brain-self-stimulation. Angyán (2, 3) found that self-stimulation produced cardiovascular and respiratory effects which varied according to the electrode site. However, in dogs, Sadowski et al. (54) did not find significant changes in arterial blood pressure or heart rate related to ICS. From those studies, it appeared that visceral changes are phenomena associated with the evoked behavioral pattern which may play an important role in timing of behavior. For instance, self-stimulation in dogs was interrupted when the temperature rose and started again, when temperature declined (53). In extension, changes in the vegetative system or at the hormonal level may organize rhythms of activity and rest, such as the circadian rhythm of self-stimulation (e.g. 71). The visceral feedback control may, however, not be evident when rates of lever-pressing are measured over short time intervals.

In a pharmacological experiment in dogs (77) we found that elicited peripheral changes in the organism might belong to a set of controlling factors conditioned to the internal S. Using the paradigm previously described, it was found that the centrally and peripherally acting anticholinergic dexetimide either antagonized or potentiated the inhibition produced by haloperidol. This effect was dependent on doses, the electrode location and the particular dog. This was an unexpected finding since dexetimide is known to reverse the haloperidol-induced inhibition of ICS in rats (see above).

The same dogs were treated with haloperidol, followed by the purely peripherally acting anticholinergic isopropamide (27). Whereas isopropamide on its own had hardly any effect on self-stimulation rates it potentiated the inhibition produced by haloperidol (or tendency to inhibition), even on those electrodes where dexetimide antagonized the haloperidol-produced inhibition. This effect was most pronounced at intermediate dose levels of haloperidol. Since isopropamide only acts as a mydriatic and antisecretory agent it was assumed that these effects are the only factors responsible for the increased response depression produced by haloperidol. The mydriatic effect was not essential since atropine (1% solution) topically applied to the eyeballs of the dogs did not potentiate the inhibition.

Peripheral phenomena in the organism appear to belong to a set of controlling factors conditioned to the internal S (see also 61). These controlling phenomena are not easily discerned in the behavior when rather crude measurements are used.

It is conceived that brain stimulation through a local phenomenon (neuronal activity) creates a general motivational state producing response facilitation (35). The behavior evoked is consequent to the appropriate environmental S (see also 69) and together with visceral feedback and peripheral elicited changes (interoceptive S) these S function as a set of conditioned S.

NEUROCHEMICAL BASES OF DRIVE AND REINFORCEMENT

The study of self-stimulation behavior switched the emphasis from a purely psychological study of motivation and reinforcement towards the physiology, anatomy and neurochemistry of reward systems. Starting from the concept of the MFB as the anatomical substrate of reward, pharmacological experiments by Stein, Poschel and Dresse, originated the catecholamine hypothesis of reward (formulated by Crow 13, 14). The hypothesis stated that ICS is sustained by two systems: the DA neurons originating in nuclei of the ventral mesencephalon and the NA neurons originating in the locus coeruleus. Much data was gathered on this hypothesis (93).

Although the pharmacological evidence that the NA system is necessary in ICS is relatively weak, no viable alternatives have been proposed. The reinforcing role for NA neurons (23) and its memory-consolidating function is, therefore, of interest.

The DA hypothesis of reward is still the most attractive and sustained by many experiments. Herein, we have surveyed some of the pharmacological evidence suggesting that intact DA neurons must be present in order to be able to carry out complex behavior.

Lesions of the basal ganglia, especially the caudate-putamen complex or the nigrostriatal pathway showed that the basal ganglia play an important role in the system of brain structures controlling behavior. More specifically, the studies suggest that they play a critical role in complex behaviour and integrate sensory input and motor output. This function allows the establishment and sequencing of behavior.

Herberg et al. (23, p. 575) suggest that "... DA pathways, implicated in other motivational activities, contribute to a state of drive or arousal necessary for self-stimulation...". This is consistent with the view that DA pathways mediate a non-specific motivational state; "which is manifested as a specific drive activity only in the presence of a corresponding reinforcer" (23). This is not remote from our suggestion that the motor activity, mediated via structures innervated by the DA pathways, plays an essential role. The psychophysiology of motivation de-emphasized the particular role played by the hypothalamus or limbic structures as those primarily concerned with drives. The role of the behavior itself and the critical role of the basal ganglia in controlling engagement with the environment is stressed.

In this respect it is important to consider the experiments by Huston and Borbély (26) suggesting that self-stimulation can still be obtained even after massive forebrain lesions, provided simple motor behaviors are used as operants.

The absence of extinction after treatment with high doses of apomorphine (or other CNS stimulants) or after forebrain lesions, suggests that behavior can be maintained as long as the drive is high, even if the adequate reinforcer is absent and, in addition, that the basal ganglia have an important information control function (also suggested in the dog experiment on haloperidol-apomorphine interaction).

Continuing along the lines of the dual model of self-stimulation proposed by Deutsch (18), Herberg et al. (23) suggested that ICS is equally dependent on both NA and DA. In their model, the reinforcement component depends in part on NA and the motivation component on DA, both have complementary roles in ICS.

In the absence of a direct DA activation (such as with locus coeruleus self-stimulation), the motivational component is low and tends to decrease activity. The latter would be the reason for the "unenthusiastic quality of locus coeruleus self-stimulation" (23, p. 580). In an optimal situation, activation of the NA reinforcing system requires also an activation of the DA motivating system. This is further not remote from the ideas on the role of drives in classical and instrumental conditioning, as proposed for instance by Konorski (29): drives produce arousal of the motor system (a function subserved by DA pathways), the reward through inhibition of the drive permits consolidation of the instrumental response (a function subserved by a NA pathway).

Further, exteroceptive S (auditory, visual or environmental situation) can control ICS. The exteroceptive S functions as a discriminative S for the behavior subsequently reinforced by the brain stimulation. The electrical stimulation, however, also elicits a number of physiological changes. Visceral feedback might be involved in the control of timing of behavior. Further, dog experiments showed that the same electrical stimulation is also able to provide respondent control of behavior. In general, brain-stimulation produces response facilitation which is adequate for response to environmental S; the behavior is further controlled by visceral feedback and peripheral changes; these form a whole set of conditioned S able to control behavior.

Finally, it appears important to remember that the concept of brain-stimulation reward is not unitary. Self-stimulation of an animal with massive forebrain lesions is essentially different from the self-stimulation in an intact animal. These differences do not solely reside in the fact that complex behavior is not possible and in the removal of structures which filter relevant information, such that extinction is lacking, but also in terms of the reward effect itself. This refers to traditional concepts of the different levels of integrative activity of the brain (56). Apparently there are different reward systems differentiated on the basis of the response specification (93, 95).

I sincerely thank David Ashton for his help during the preparation of this study. This paper is based on a lecture given at the Department of Neurophysiology, Nencki Institute, Warsaw, 6 June 1979.

REFERENCES

1. ANDÉN, N. E., DAHLSTRÖM, A., FUXE, K., LARSSON, K., OLSON, C. and UNGERSTEDT, U. 1966. Ascending monoamine neurones to the telencephalon and diencephalon. Acta Physiol. Scand. 67. 313–326.
2. ÁNGYÁN, L. 1976. Autonomic effects of self-stimulation. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 461–466.
3. ÁNGYÁN, L. 1978. Cardiovascular effects of septal, thalamic, hypothalamic and midbrain self-stimulation. Physiol. Behav. 20: 217–226.
4. BALL, G. G. 1974. Vagotomy: effect of electrically elicited eating and self-stimulation in the lateral hypothalamus. Science 184: 484–485.
5. BARTHOLINI, G. and PLETSCHER, A. 1971. Atropine-induced changes of cerebral dopamine turnover. Experientia 27: 1302–1303.
6. CLAVIER, R. M. 1976. Brain stem self-stimulation catecholamine or non-catecholamine mediation? *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 239–250.
7. COOLS, A. R. 1973. The caudate nucleus and neurobiochemical control of behaviour. The function of dopamine and serotonin in the caput nuclei caudati of cats. Nijmegen, Drukkerij Brakkenstein.
8. COOLS, A. R. and VAN ROSSUM, J. M. 1976. Excitation-mediating and inhibition-mediating dopamine receptors: a new concept towards a better understanding of electrophysiological, biochemical, pharmacological, functional and clinical data. Psychopharmacologia 45: 243–254.
9. COSTALL, B., NAYLOR, R. J., CANNON, J. G. and LEE, T. 1977. Differential action by some 2-aminotetralin derivatives of the receptor mechanisms in the nucleus accumbens of rat which mediate hyperactivity and stereotyped biting. Eur. J. Pharmacol. 41: 307–319.
10. COSTALL, B., NAYLOR, R. J. and NEYMEYER, J. L. 1975. Differences in the nature of the stereotyped behaviour induced by apophine derivatives in the rat and in their interactions in extrapyramidal and mesolimbic brain areas. Eur. J. Pharmacol. 31: 1–16.
11. COSTALL, B., NAYLOR, R. J. and NEUMEYER, J. C. 1975. Dissociation of the aporphine derivatives of the stereotypic and hyperactivity responses resulting from injections into the nucleus accumbens septi. J. Pharm. Pharmacol. 27: 875–877.
12. CROW, T. J. 1971. The relation between electrical self-stimulation sites and

catecholamine-containing neurones in the rat mesencephalon. Experientia (Basel) 27: 662.

13. CROW, T. J. 1972. Catecholamine-containing neurones and electrical self-stimulation. Part 1 (A review of somedata). Psychol. Med. 2: 414.
14. CROW, T. J. 1973. Catecholamine-containing neurones and electrical self-stimulation. II. A theoretical interpretation and some psychiatric implications. Psychol. Med. 3: 66–73.
15. CROW, T. J. 1976. Specific monoamine systems as reward pathways: evidence for the hypothesis that activation of the ventral mesencephalic dopaminergic neurones and noradrenergic neurones of the locus coeruleus complex will support self-stimulation responding. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 211–237.
16. CROW, J. F. and DEAKIN, J. F. W. 1978. Brain reinforcement centers and psychoactive drugs. *In* V. Y. Israel, F. B. Glaser, H. Kalant, R. E. Popham, W. Schmidt and R. G. Smart (ed.), Research advances in alcohol and drug problems. Plenum Publishing Co., New York, p. 25–76.
17. DAHLSTRÖM, A. and FUXE, K. 1964. Evidence for the existence of monoamine containing neurones in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurones. Acta Physiol. Scand. 62, Suppl. 232.
18. DEUTSCH, J. A. 1960. The structural basis of behaviour. Univ. Chicago Press, Chicago, 186 p.
19. DRESSE, A. 1966. Importance du système mésencéphalo-télencéphalique noradrénergique comme substratum anatomique du comportement d'autostimulation. Life Sci. 5: 1003–1014.
20. FRANKLIN, K. B. J., STEPHENS, D. N. and HERBERG, L. J. 1976. Even "dopaminergic" self-stimulation requires noradrenergic activity. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 264–266.
21. GLICKMAN, S. E. and SCHIFF, B. B. 1967. A biological theory of reinforcement. Psychol. Rev. 74: 81–109.
22. HERBERG, G. J. and STEPHENS, D. N. 1975. Catecholamines and self-stimulation: the action of amantadine and its interaction with amphetamine. Pharmacol. Biochem. Behav. 3: 263–269.
23. HERBERG, L. J., STEPHENS, D. N. and FRANKLIN, K. B. J. 1976. Catecholamines and self-stimulation, evidence suggesting a reinforcing role for noradrenaline and a motivating role for dopamine. Pharmacol. Biochem. Behav. 4: 575–582.
24. HOROVITZ, Z. P., CHOW, M. I. and CARLTON, P. L. 1962. Self-stimulation of the brain by cats: effects of imipramine, amphetamine and chlorpromazine. Psychopharmacology 3: 455–462.
25. HULL, C. L. 1952. A behaviour system. John Wiley and Sons, New York.
26. HUSTON, J. R. and BORBÉLY, A. A. 1973. Operant conditioning in forebrain ablated rats by use of rewarding hypothalamic stimulation. Brain Res. 50: 467–472.
27. JANSSEN, P. A. J. and NIEMEGEERS, C. J. E. 1967. The peripheral and anticholinergic properties of benzetimide (R 4929) and other atropine-like drugs as measured in a new anti-pilocarpine test in rats. Psychopharmacologia 11: 231–254.

28. JANSSEN, P. A. J., NIEMEGEERS, C. J. E. and SCHELLEKENS, K. H. L. 1965. Is it possible to predict the clinical effect of neuroleptic drugs (major tranquillizers) from animal data? Part I. "Neuroleptic activity spectra" for rats. Arzneim. Forsch. 15: 104–117.
29. KONORSKI, J. 1974. Classical and instrumental conditioning: the general laws of connections between "centers". Acta Neurobiol. Exp. 34: 5–13.
30. LENZER, I. I. and FROMMER, G. P. 1968. Successive sensory discriminative behaviour maintained by intracranial self-stimulation reinforcement. Physiol. Behav. 3: 345–349.
31. LINDVALL, O. and BJÖRKLUND, A. 1974. The organization of the ascending catecholamine neurons-systems in the rat brain. Acta Physiol. Scand. 92, Suppl. 412.
32. LINDVALL, O., BJÖRKLUND, A., MOORE, K. Y. and STEVENI, V. 1974. Mesencephalic dopamine neurons projecting the neocortex. Brain Res. 81: 332–337.
33. LORENS, S. A. 1976. Anatomical substrate of intracranial self-stimulation: contribution of lesion studies. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation. North-Holland Publishing Co., Amsterdam, p. 41–50.
34. MILLHOUSE, O. E. 1969. A Golgi study of the descending medial forebrain bundle. Brain Res. 15: 341–363.
35. MILNER, P. 1976. Models of motivation and reinforcement. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 543–556.
36. MOGENSON, G. and CIOÉ, J. 1977. Central reinforcement: a bridge between function and behaviour. *In* W. K. Honig and J. E. R. Stadden (ed.), Handbook of operant behaviour. Englewood Cliffs, Prentice Hall, New York, p. 570–595.
37. MOGENSON, G. J. and PHILLIPS, A. G. 1976. Motivation: a psychological construct in search of a physiological substrate. *In* Progress in psychobiology and physiological psychology. Vol. 6. Academic Press, New York, p. 189–243.
38. MORA, F. 1978. The neurochemical substrates of prefrontal cortex self-stimulation: a review and an interpretation of some recent data. Life Sci. 22: 919–930.
39. NIEMEGEERS, C. J. E., LENAERTS, F. M., ARTOIS, K. S. K. and JANSSEN, P. A. J. 1977. Interaction of drugs with apomorphine, tryptamine and norepinephrine. A new "in vivo" approach: the ATN-test in rats. Arch. Int. Pharmacodyn. Ther. 227: 407–422.
40. NIEMEGEERS, C. J. E., VERBRUGGEN, F. J., WAUQUIER, A. and JANSSEN, P. A. J. 1972. The influence of haloperidol and amphetamine on two different noise-escape situations in rats. Psychopharmacologia 25: 22–31.
41. OLDS, J. 1973. Brain mechanisms of reinforcing learning. *In* D. E. Berlyne and K. B. Madsen (ed.), Pleasure, reward, preference. Academic Press, New York, p. 35–63.
42. OLDS, J. 1976. Reward and drive neurons: 1975. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 1–27.
43. OLDS, J. and MILNER, P. 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of the rat brain. J. Comp. Physiol. Psychol. 47: 419–427.

44. OLDS, M. E. and OLDS, J. 1963. Approach-avoidance analysis in rat diencephalon. J. Comp. Neurol. 120: 259–295.

45. PAVLOVA, O., KOSOWSKI, S. and SADOWSKI, B. 1976. Conditioning of self-stimulation in the dog to acoustic and visual stimuli. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 403–405.

46. PHILLIPS, A. G., CARTER, D. A. and FIBIGER, H. C. 1976. Decreased intracranial self-stimulation after neuroleptics or destruction of the nigrostriatal bundle: performance or reinforcement deficit? *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward: North-Holland Publishing Co., Amsterdam, p. 272–279.

47. ROBERTS, E. 1974. Disinhibition as an organizing principle in the nervous system. The role of gamma-aminobutyric acid. *In* F. McDowell and A. Barbeau (ed.), Advances of neurology. Vol. 5. Raven Press, New York, p. 127–143.

48. ROLL, S. K. 1970. Intracranial self-stimulation and wakefulness: effect of manipulating ambient brain catecholamines. Science 168: 1370–1372.

49. ROLLS, E. T., ROLLS, B. J., KELLY, P. H., SHAW, S. G. and DALE, R. 1974. The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade. Psychopharmacologia 38: 219–230.

50. ROUTTENBERG, A. 1976. Self-stimulation pathways: origins and terminations. A three stage technique. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward North-Holland Publishing Co., Amsterdam, p. 31–39.

51. SADOWSKI, B. 1974. Negativism to food during self-stimulation in the anterior part of the basal forebrain in dogs. Physiol. Behav. 13: 645–651.

52. SADOWSKI, B. 1976. Physiological correlates of self-stimulation. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 434–460.

53. SADOWSKI, B., BRZEZINSKA, Z. and KACIUBA-USCISŁKO, H. 1976. On the mechanism of hyperthermia during self-stimulation: a possible role of nervous and humoral factors. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 467–471.

54. SADOWSKI, B., WAUQUIER, A., JAGENEAU, A. and JANSSEN, P. A. J. 1979. Arterial blood pressure and heart rate changes during self-stimulation by dogs in the basal forebrain region, lateral preoptic area, hypothalamus, ventral midbrain and amygdala. J. Physiol. (Paris) 75: 255–267.

55. SHEFFIELD, F. D. 1968. A drive-induction theory of reinforcement. *In* R. W. Haber (ed.), Current research in motivation. Holt, Rhinehart and Winston, New York.

56. SHERRINGTON, C. S. 1906. The integrative action of the nervous system, C. Scribner's, New York, p. 433.

57. SPENCE, K. W. 1956. Behaviour theory and conditioning. Yale University Press, New Haven.

58. STARK, P. 1964. Some neurohormones affecting hypothalamic self-stimulation. Thesis, Ann. Arbor Michigan, University Microfilms.

59. STEIN, L. 1964. Self-stimulation of the brain and the central stimulant action of amphetamine. Fed. Proc. 23: 836–850.

60. STEIN, L., BELLUZZI, J. D. and WISE, C. D. 1976. Norepinephrine self-stimulation pathways: implications for long-term memory and schizophrenia. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co. Amsterdam, p. 297–331.

61. STEIN, L., BELLUZZI, J. D. and WISE, C. D. 1977. The physiology of operant behaviour. *In* I. Hanin and E. Usdin (ed.), Animal models in psychiatry and neurology. Pergamon Press, Oxford, p. 9–17.

62. STEPHENS, D. and HERBERG, C. J. 1979. Dopamine-acetylcholine "balance" in nucleus accumbens and corpus striatum and its effects on hypothalamic self-stimulation. Eur. J. Pharmacol. 54: 331–339.

63. THIERRY, A. M., BLANC, Y., SOBEL, A., STINUS, C. and GLOWINSKI, J. 1973. Dopaminergic terminal in the rat cortex. Science 182: 499–501.

64. THIERRY, A. M., TASSIN, J. P., BLANC, C. and GŁOWINSKI, J. 1976. Topographic and pharmacological study of the mesocortical dopaminergic system. *In* Brain-stimulation reward. A. Wauquier and E. T. Rolls (ed.), North-Holland Publishing Co., Amsterdam, p. 290–293.

65. THORNDIKE, E. L. 1933. A theory of the actions of the after-effects of a connection upon it. Psychol. Rev. 40: 434.

66. TROWILL, J. A., PANKSEPP, J. and GANDELMAN, R. 1969. An incentive model of rewarding brain stimulation. Psychol. Rev. 76: 264–281.

67. UNGERSTEDT, U. 1971. Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol. Scand., Suppl. 367, 1–48.

68. VALENSTEIN, E. S. 1966. The anatomical laws of reinforcement. *In* E. Stellar and J. M. Sprague (ed.), Progress in physiological psychology. Vol. 1. Academic Press, New York, p. 149–190.

69. VALENSTEIN, E. S. 1976. The interpretation of behaviour evoked by brain-stimulation. *In* A. Wauquier and E. T. Rolls (ed.), Brain stimulation reward. North-Holland Publishing Co., Amsterdam, p. 557–575.

70. WARD, J. W. and HESTER, R. W. 1969. Intracranial self-stimulation in cats surgically deprived of autonomic outflows. J. Comp. Physiol. Psychol. 67: 336–343.

71 WAUQUIER, A. 1974. Circadian rhythm of brain self-stimulation in rats and resistance to long-term effects of psychopharmacological substances. J. Interdiscipl. Cycle. Res. 5: 340–346.

72. WAUQUIER, A. 1975. Brain self-stimulation in dogs: the influence of haloperidol, pimozide and pipamperone. Sixth International Congress of Pharmacology. Helsinki, 821 (Abstr.).

73. WAUQUIER, A. 1976. The influence of psychoactive drugs on brain self-stimulation in rats: a review. *In* A. Wauquier and E. T. Rolls (ed.), Brain-stimulation reward. North-Holland Publishing Co., Amsterdam, p. 123–170.

74. WAUQUIER, A. 1977. The interaction of receptor blockers on the apomorphine-induced enhancement and inhibition of lever pressing for brain stimulation. J. Pharmacol. 8: 567.

75. WAUQUIER, A. 1978. Neuroleptics and brain self-stimulation behaviour. Int. Rev. Neurobiol. 21: (in press).

76. WAUQUIER, A. 1978. Differential actions of dopamine agonists on brain self-stimulation behaviour in rats. Arch Int. Pharmacodyn. 236: 325–328.

77. WAUQUIER, A. 1978. Internal stimulus conditioning to discriminative external stimuli. *In* F. C. Colpaert and J. A. Rosencrans (ed.), Stimulus properties

of drugs: ten years of progress. North-Holland Publishing Co., Amsterdam, p. 535–550.

78. WAUQUIER, A. 1979. Basal ganglia: control function in instrumental behaviour. Appl. Neurophysiol. 42: 103–105.
79. WAUQUIER, A., MELIS, W., NIEMEGEERS, C. J. E. and JANSSEN, P. A. J. 1978. A putative multipartite model of haloperidol interaction in apomorphine disturbed behaviour of the dog. Psychopharmacology 59: 255–258.
80. WAUQUIER, A., MELIS, W. and SADOWSKI, B. 1977. Brain-stimulation reward in the dog: behavioural, vegetative and pharmacological effects. 27th Int. Congress of Physiology, Paris. p. 802 (Abstr.).
81. WAUQUIER, A. and NIEMEGEERS, C. J. E. 1972. Intracranial self-stimulation in rats as a function of various stimulus parameters. II. The influence of haloperidol, pimozide and pipamperone on medial forebrain bundle stimulation with monopolar electrodes. Psychopharmacologia 27: 191–202.
82. WAUQUIER, A. and NIEMEGEERS, C. J. E. 1973. Intracranial self-stimulation in rats as a function of various stimulus parameters. III. The influence of apomorphine on medial forebrain bundle stimulation with monopolar electrodes. Psychopharmacologia 30: 163–172.
83. WAUQUIER, A. and NIEMEGEERS, C. J. E. 1974. Intracranial self-stimulation in rats as a function of various stimulus parameters. IV. The influence of amphetamine on medial forebrain bundle stimulation with monopolar electrodes. Psychopharmacologia 34: 265–274.
84. WAUQUIER, A. and NIEMEGEERS, C. J. E. 1974. Intracranial self-stimulation in rats as a function of various stimulus parameters. V. Influence of cocaine on medial forebrain bundle stimulation with monopolar electrodes. Psychopharmacologia 38: 201–210.
85. WAUQUIER, A. and NIEMEGEERS, C. J. E. 1975. The effects of dexetimide on pimozide-, haloperidol- and pipamperone-induced inhibition of brain self-stimulation in rats. Arch. Int. Pharmacodyn. Ther. 217: 280–292.
86. WAUQUIER, A. and NIEMEGEERS, C. J. E. 1976. Bromperidol: a potent inhibitor of intracranial self-stimulation in rats. Arzneim. Forsch. 26: 1356–1359.
87. WAUQUIER, A. and NIEMEGEERS. C. J. E. 1976. Restoration of self-stimulation inhibited by neuroleptics. Eur. J. Pharmacol. 40: 191–194.
88. WAUQUIER, A. and NIEMEGEERS, C. J. E. 1979. A comparison between lick- or lever-pressing contingent reward and the effects of neuroleptics thereon. Arch. Int. Pharmacodyn. Ther. 239: 230–240.
89. WAUQUIER, A., NIEMEGEERS, C. J. E. and GEIVERS, H. A. 1972. Intracranial self-stimulation in rats as a function of various stimuli parameters. I. An empirical study with monopolar electrodes in the medial forebrain bundle. Psychopharmacologia 23: 238–260.
90. WAUQUIER, A., NIEMEGEERS, C. J. E. and LAL, H. 1974. Differential antagonism by naloxone of inhibitory effects of haloperidol and morphine on brain self-stimulation. Psychopharmacologia 37: 303–310.
91. WAUQUIER, A., NIEMEGEERS, C. J. E. and LAL, H. 1975. Differential antagonism by the anticholinergic dexetimide of inhibitory effects of haloperidol and fentanyl on brain self-stimulation. Psychopharmacologia 41: 229–235.

92. WAUQUIER, A., NIEMEGEERS, C. J. E. and LAL, H. 1976. Selective reversal of haloperidol-induced inhibition of brain self-stimulation by the anticholinergic dexetimide. *In* P. B. Bradley and B. N. Dhawan (ed.), Drugs and central synaptic transmission. The MacMillan Press Ltd., London, p. 201–209.
93. WAUQUIER, A. and ROLLS, E. T. (ed.) 1976. Brain-stimulation reward. North Holland Publishing Co., Amsterdam, 622 p.
94. WHITE, N. 1976. Strength-duration analysis of the organization of reinforcement pathways in the medial forebrain bundle of rats. Brain Res. 110: 575–591.
95. WHITE, N., BROWN, Z. and YACHNIN, M. 1978. Effects of catecholamine manipulations of three different self-stimulation behaviours. Pharmacol. Biochem. Behav. 9: 603–608.
96. WISE, R. A. 1978. Catecholamine theories of reward: a critical review. Brain Res. 152: 215–247.

Accepted 10 January 1980

A. WAUQUIER, Department of Pharmacology, Janssen Pharmaceutica, Turnhoutsebaan 30, B-2340 Beerse, Belgium.