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Self-Stimulation of the Nucleus Accumbens and Some Comparisons with Hypothalamic Self-Stimulation

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JENKINS, O. F., D. M. ATRENS AND D. M. JACKSON. *Self-stimulation of the nucleus accumbens and some comparisons with hypothalamic self-stimulation.* PHARMACOL BIOCHEM BEHAV 18(4) 585–591, 1983.—Rats were trained to respond for electrical stimulation of the nucleus accumbens (ACB) or lateral hypothalamus (HYP) in a shuttle-box apparatus. Whereas the HYP rats showed rapid acquisition and stabilization of performance, the ACB rats were slow to learn the task and commonly took longer than 20 daily sessions to stabilize. Once stabilized, both groups responded with similarly vigorous performance. All rats displayed a predominantly locomotor behaviour, which was almost totally devoid of exploratory behaviours typically associated with self-stimulation. The absence of stimulus-bound behaviours was particularly notable in the ACB group. These rats, but not the HYP rats, showed an increase in the latency to initiate stimulation during the daily 25-min test sessions. Depriving the animals of a single self-stimulation session caused a decrease in the latency of ACB rats to initiate on the following day while having no effect on the HYP rats. All ACB rats gradually developed convulsive seizures during the first 3 weeks of testing which subsequently became more frequent and severe. None of the HYP rats showed any involuntary motor effects. The results show that ACB self-stimulation is a very different phenomenon to HYP self-stimulation, and suggest that, in addition to reward and aversion, ACB self-stimulation may involve a stereotyped ritual controlled partly by adaptation and conditioning.

Nucleus accumbens Hypothalamus Shuttle-box Initiation Escape Clonic seizure Stereotyped ritual

THE observation that rats will perform a task to obtain intracranial electrical stimulation has been generally accepted as indicating that the stimulation has rewarding properties. The hypothalamus has long been considered the area supporting the most vigorous responding and is thus presumed to be the most rewarding area [2,3]. However, there is a large and growing literature on positive self-stimulation sites in many brain areas (for references, see [7,8]). Since these areas have diverse functions, it is possible that some of these sites support self-stimulation behaviour for reasons other than that of obtaining rewarding sensations. In support of this, it is interesting to note that rats will repeatedly turn on and off any appropriate stimulus placed under their control [15].

Catecholamines have been widely associated with self-stimulation behaviour [8] and for this reason some workers have examined electrode sites in the dopamine-rich areas of the neostriatal (e.g., [20]) and mesolimbic (e.g., [2, 19, 21, 24, 26]) systems. The nucleus accumbens (ACB) is densely innervated with dopamine terminals [17] and is of prime importance in the control of motor performance and locomotor activity [1,13]. Since one of the major problems associated with experiments on self-stimulation is to distinguish between effects on reward and on motor performance [7], the ACB is one of the more interesting areas to study.

The ability of the ACB to support self-stimulation behaviour has been the subject of a number of investigations utilizing a variety of operant tasks (e.g., [2, 19, 21, 24, 26]). Some of these studies, however, did not report the basic behavioural characteristics (e.g., baseline response rates, ease of training and stabilization, involuntary motor effects and stimulus-bound behaviours) which usually accompany self-stimulation responses. The present study is an investigation into the basic characteristics of ACB self-stimulation with some direct comparisons to hypothalamic self-stimulation using the same model. The shuttle box technique was used because it requires a locomotor response [12]. Moreover, it provides an index of reward which can be dissociated from motor performance effects [3,12].

METHOD

Animals and Equipment

The subjects were male Wistar rats (University of Sydney Animal House) weighing 300–400 g at the time of surgery. Following surgery, the rats were individually housed in polypropylene cages (40×24×16 cm). The colony was maintained at a constant temperature (21±1°) on a 15 hr light/9 hr dark cycle (0630–2130 light). Free access to food (Allied

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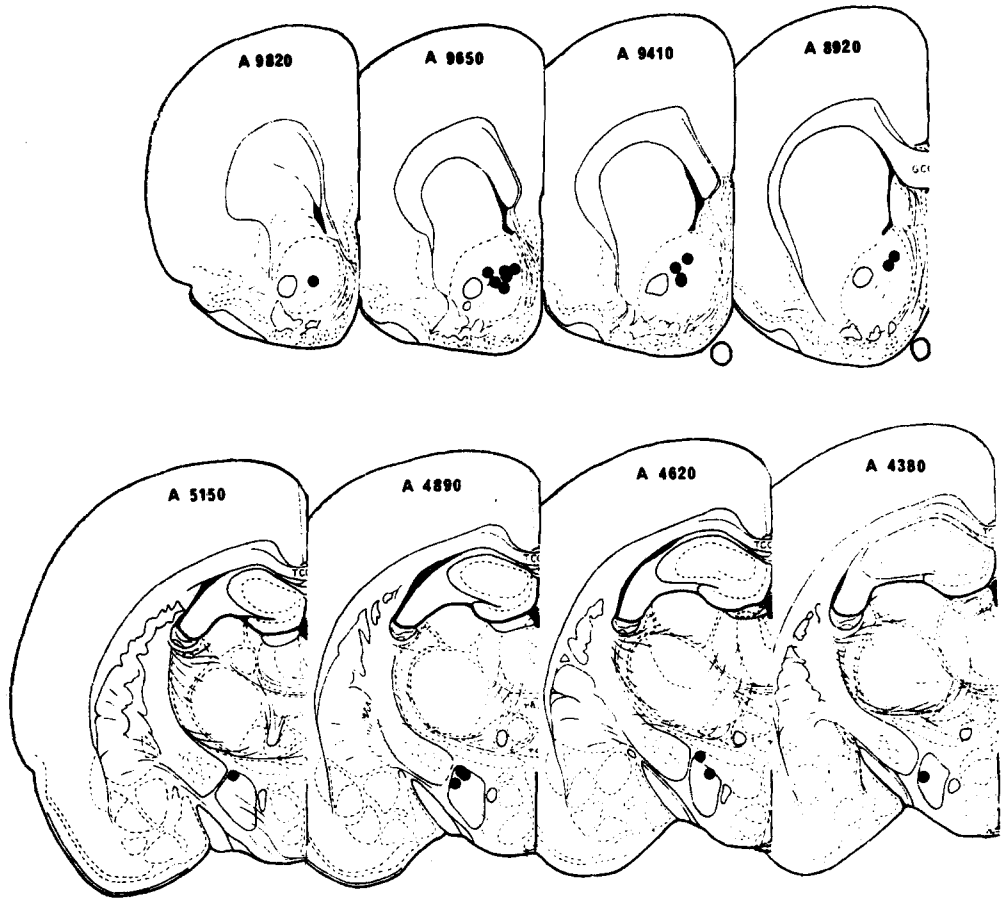

FIG. 1. Schematic diagram adapted from the atlas of König and Klippel [16] showing electrode sites in the ACB and HYP.

Feeds, Sydney) and tap water was allowed except during self-stimulation testing.

The self-stimulation chambers consisted of four shuttle-boxes as described previously [12]. The stimulation was delivered as current-regulated 100 Hz biphasic rectangular pulses of 200 μsec duration. The anodal pulse followed each cathodal pulse by 5 msec. Rats controlled the stimulation by means of two photobeams, one at either end of the shuttle-box. Breaking the "on" photobeam initiated a continuous train of stimulation which could be terminated by breaking the photobeam at the opposite end of the box. The mean latencies to initiate and escape the stimulation were recorded electronically. If an animal did not make a response within 60 sec, the stimulation was switched on (or off) automatically.

Electrode Implantation and Histology

Rats were anaesthetised with Pentathesin (Parnell Laboratories, Sydney) (2 ml/kg) and placed in a Kopf stereotaxic instrument. Monopolar platinum-iridium (90%–10%) electrodes (254 μm diameter) (California Fine Wire Co.) which were insulated except for the flat cross-sectional area of the tip, were implanted unilaterally into either the ACB or the lateral hypothalamic component of the medial forebrain bundle (HYP). Current return was achieved via one of four stainless-steel screws embedded in the skull. The stereotaxic coordinates relative to bregma (flat skull position) were: anterior 2.2, lateral 1.3 and dorsoventral −6.8 for the ACB placements, and posterior 2.8, lateral 1.6 and dorsoventral −8.2 for the HYP placements. Animals were allowed at least 5 days recovery before any self-stimulation testing was begun.

Following experimentation, the brains were removed, frozen to −12° and 40 μm sections cut in an American Optical microtome. The tissue was mounted on glass slides and stained with toluidine blue for examination of electrode sites. Some of the brains were first fixed in 10% formalin/saline solution, mounted on gelatin-coated slides, and stained in the same manner. Verification of placements was made with reference to the atlas of König and Klippel [16].

Procedure

Animals were trained in daily sessions of 30–60 min, 5–7 days/week (mean=6), between 12 noon and 7 p.m., and individual rats were run at the same time each day (±30 min). As the rats began to stabilize (0–3 weeks), the session length was standardised to 25 min consisting of 3 time intervals (0–5, 5–15 and 15–25 min) during which mean latencies were recorded. The stimulating current was altered during the training period to determine the most suitable current for each rat. Subsequently each rat was maintained on a constant current (range 250–400 μA).

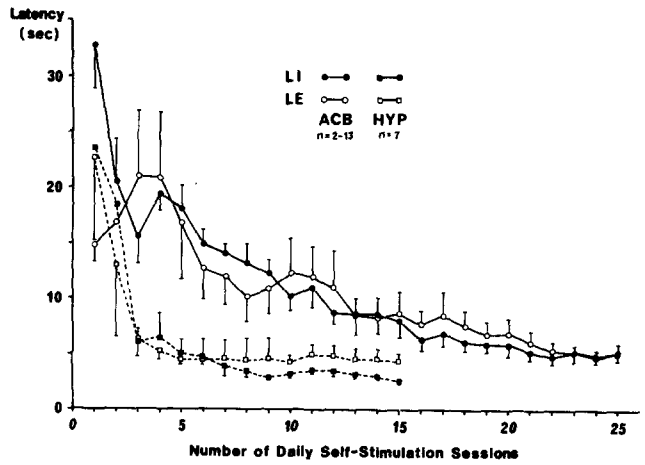

FIG. 2. Mean latencies (±SEM) to initiate (LI) and escape (LE) shuttle-box self-stimulation of the ACB or HYP as a function of the number of daily test sessions. Due to the initially poor performance of the ACB rats, the responses made during the first few sessions were not recorded for some rats. This resulted in the variation of the value of n. The session length for the ACB rats during the first 10 sessions varied from 25 min to 60 min. In all other cases it was standardised to 25 min. The result for each rat is a mean of the responses made over the whole session. These individual means were used to calculate the final mean and SEM for each group of rats.

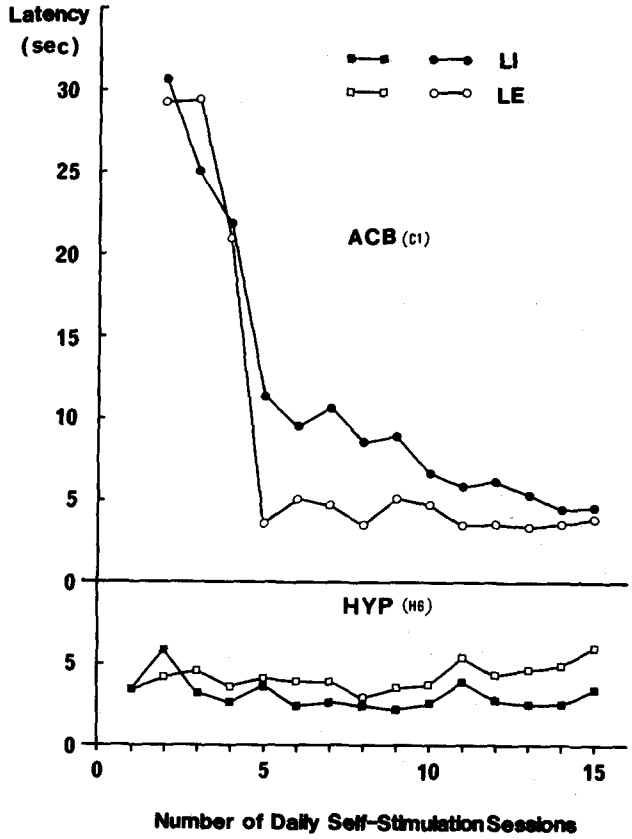

FIG. 3. Individual mean latencies to initiate and escape for 2 rats which were the most vigorous performers of the ACB and HYP groups, over the first 15 test sessions. The responses of the ACB rat in the first test were not recorded.

Statistical Analysis

The results were analysed by multifactor Analyses of Variance with repeated measures, Students' *t*-tests or paired *t*-tests.

RESULTS

Electrode Placements

All ACB electrodes were found to be located in the anterior nucleus accumbens slightly medial and dorsal to the anterior commissure (Fig. 1). The HYP electrodes were located in or adjacent to the medial forebrain bundle in the lateral hypothalamic area (Fig. 1). The results from animals in which the electrode placements were inaccurate were discarded.

Training and Response Rates

All rats with correctly placed electrodes acquired the ability to perform the shuttle-box task and all displayed high response rates (short latencies). To attain this level of responding, extensive training was required for the ACB rats, while the HYP animals learned the task after only minimal testing. Figure 2 shows the changes in the mean latencies to initiate and escape stimulation in ACB and HYP rats over a period of 15 to 25 daily test sessions. The acquisition of vigorous performance was very rapid in the HYP rats, both latencies reaching about 5 sec by the third day. Subsequent stabilization occurred quickly. In contrast, the ACB animals began responding slowly and showed a gradual decrease in both latencies as they gained experience. It took more than 20 days for these rats to perform as vigorously as the HYP rats did in 3 days. Even the best performer of the ACB rats (Fig. 3) took a considerable time to stabilize after a gradual shortening of latencies. Figure 3 also shows the best HYP rat with its almost immediate stabilization at a high level of performance. This pattern of acquisition occurred in 3 out of 7 HYP rats but in none of the ACB rats.

Despite the initially poor performance of the ACB rats and their slow stabilization, it is interesting to note that once stabilized they responded just as vigorously as the HYP rats (Table 1). There were no differences in the initiation or escape latencies between the two groups (Students' *t*-test). Note however, that in both groups the escape latencies were slightly longer than the initiation latencies, although this effect was not significant (paired *t*-test).

In stabilized rats, the time course of responding over the 25-min session was different in the two groups (Table 2). The overall results of a 3 factor Analysis of Variance showed that there was a significant difference between the latencies, $F(1,14)=8.361, p<0.025$, but not between the electrode sites, $F(1,14)=0.307$, or over time, $F(2,28)=1.134$. However there were significant interactions between time and the other two factors, and analysis of the simple effects of time revealed that there was a significant increase in the latency to initiate over the 25 min period in the ACB group, $F(2,80)=6.444$,

TABLE 1

MEAN* STABILIZED LATENCIES (±SEM) DURING 25-MIN SELF-STIMULATION SESSIONS (SEC)

Latency	ACB n=9	HYP n=7
Initiation	3.12 ± 0.30	2.54 ± 0.20
Escape	3.99 ± 0.48	3.93 ± 0.64

*Mean data were calculated from the results of individual rats for single, daily, 25-min sessions drawn at random after stabilization.

TABLE 2

MEAN* WITHIN-SESSION LATENCIES (± SEM) RECORDED DURING ONE 5- AND TWO 10-MIN PERIODS (SEC)

Latency	Time during session (min)	ACB n=9	HYP n=7
Initiation	0–5	2.12 ± 0.19	2.99 ± 0.33
	5–15	2.82 ± 0.25	2.46 ± 0.17
	15–25	5.00 ± 1.17	2.43 ± 0.24
Escape	0–5	4.71 ± 0.53	4.57 ± 0.90
	5–15	3.78 ± 0.39	4.21 ± 0.67
	15–25	3.93 ± 0.57	2.89 ± 0.57

*Calculated from the results of individual stable rats for single, daily sessions chosen at random.

TABLE 3

MEAN* LATENCIES (±SEM) OF 9 ACB RATS OVER A PERIOD OF 56 25-MIN SESSIONS AFTER INITIAL STABILIZATION (SEC)

Approximate time after stabilization (No. of daily tests)	Initiation	Escape
14	3.23 ± 0.34	3.96 ± 0.43
28	2.58 ± 0.22	3.48 ± 0.42
42	2.56 ± 0.22	3.32 ± 0.27
56	2.86 ± 0.36	3.41 ± 0.27

*Calculated from the results of individual rats for single sessions chosen at random after approximately 14, 28, 42 or 56 sessions.

$p<0.005$. No change occurred in the escape latency of these rats nor in either latency of the MFB rats, F(2.80)=0.712, 0.282 and 0.331, respectively. These results are taken as indicating a decrease in performance of the ACB rats during the session.

The responses of the ACB rats were very stable over a prolonged period of time. Table 3 shows the mean latencies of 9 rats over a period of about 2 months during which time there was only a slight decrease, Analysis of Variance, effect of time, F(3,48)=3.747, $p<0.025$. There was no significant difference between the latencies, F(1,16)=3.723, and no interaction, F(3,48)=0.222. Some rats remained stable for up to 6 months before they lost their electrodes or developed severe motor effects. Although no long-term data are available for the HYP rats, these also remain stable for a considerable period (Atrens and Hunt, unpublished observations).

Behavioural Observations

Stimulus-bound behaviours. The most common type of behaviour occurring during self-stimulation is exploration [14], although many other elicited behaviours have been noted (for references, see [4]). In the present study, the behavioural characteristics of the two groups of rats were similar in some respects. During training while the response rates were slow, the behaviour showed typical exploratory characteristics: sniffing, rearing, grooming and locomotion. As the vigour of responding increased and began to stabilize, these behaviours diminished in both groups, being replaced by a compulsive locomotion. The absence of stimulus-bound sniffing, rearing and exploration was quite marked in the ACB group. The HYP rats, while displaying a fairly similar locomotor response, showed a slightly different quality of behaviour by also engaging in intermittent stimulus-bound behaviours.

Involuntary motor effects. All the ACB rats, but none of the HYP rats, showed involuntary motor effects. These occurred as a result of long trains of stimulation and consisted, at first, of wet-dog shakes which eventually developed into full clonic seizures. Like the acquisition of shuttling behaviour, these effects developed gradually over a period of about 3 weeks. Subsequently the seizures became more frequent and severe but could be minimised by giving each animal several short bursts of stimulation at the beginning of each session. This procedure usually protected against seizures for the remainder of the session, thus ensuring minimal disruption to behavioural responses. Reducing the current intensity also reduced seizures to some extent, but resulted in large decreases in performance and stability as described in the next section.

Latency-Intensity Function

Changes in current intensity affect the responding of rats for hypothalamic stimulation [10,23]. A similar picture was observed here in response to ACB stimulation. Figure 4 shows that the responses of 6 ACB rats (which were stabilized at the same current intensity, 300 μA) were significantly affected by changes of up to 100 μA in current intensity, F(2,19)=43.055, $p<0.025$. Despite the trend, there was no significant difference between the latencies, F(1,10)=0.577, and no interaction, F(2,19)=1.958. It is interesting to note that, although the rats appeared to be responding at an almost ceiling level, increasing the current could facilitate performance.

Stimulation Deprivation

Following a single day without access to stimulation, the ACB rats responded with a significant decrease in the latency to initiate (Fig. 5). This enhanced performance occurred without any concomitant change in escape latency. Stimulation deprivation was without effect on the responses of the HYP animals.

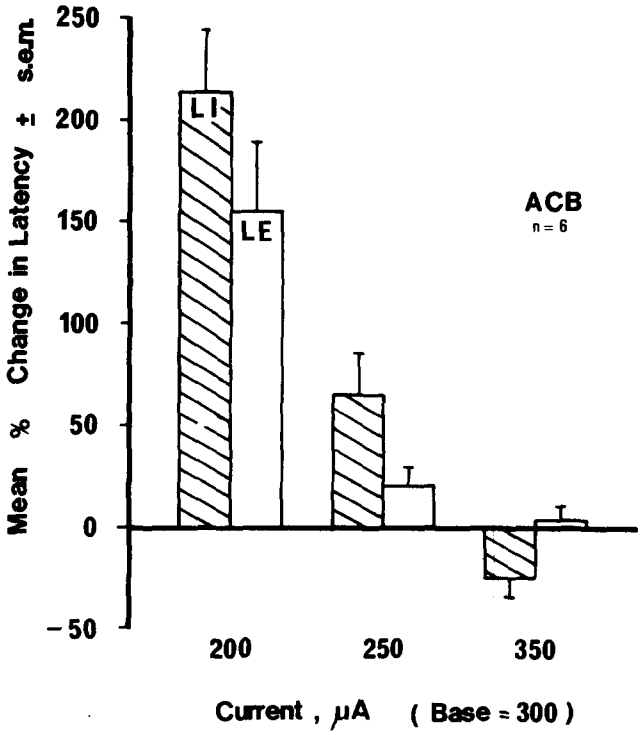

FIG. 4. The latency-intensity function for rats self-stimulating in the ACB. All rats were stabilized on a current of 300 μA and on the test day were run at either 200 (−100), 250 (−50) or 350 (+50) μA. The data are expressed as the mean % change in the latencies to initiate (shaded columns) and escape (open columns) from the test day to the control day (the previous day) over the 25-min session. The three manipulations were presented in a random order and never less than 48 hr apart.

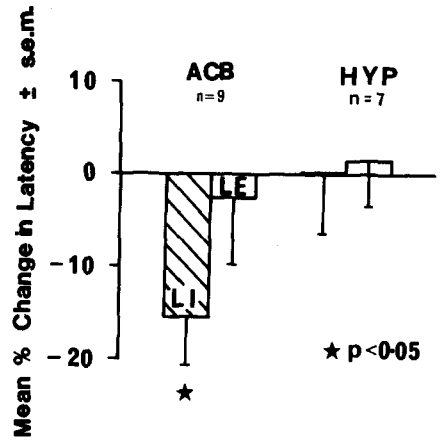

FIG. 5. The effect of depriving ACB and HYP rats of a single self-stimulation session after they had been stabilized on once-daily sessions. The results are expressed as the mean % change in latency from the baseline response (48 hr earlier). The differences between the latencies and the baseline were analysed using paired t-tests.

DISCUSSION

The present results show that the ACB in the rat can support self-stimulation, in agreement with previous studies [2, 19, 21, 24, 26]. However, several lines of evidence indicate that ACB self-stimulation is different to that maintained in the hypothalamus. The ACB animals required considerable experience before a stable level of performance was achieved, in contrast to the rapid acquisition and stabilization displayed by animals self-stimulating from the HYP (Fig. 2). The gradual decline in initiation and escape latencies and the eventual attainment of high response rates after 2–4 weeks of training has not previously been reported in the literature. Although hypothalamic self-stimulation is generally considered to be more rewarding (or more reinforcing) than stimulation of most other positively reinforcing sites [2,3], the present data show that the ACB can support performance as vigorous as that obtained from the HYP (Table 1).

Substantial seizure activity during mesolimbic and neostriatal self-stimulation has only seldom been reported in the literature [2,20]. The frequency of seizures observed here was probably due to the much longer trains of stimulation received in the shuttle-box compared to the more commonly utilised lever-pressing procedure, but this was not sufficient to cause seizures in the HYP rats. It is noteworthy that the seizures developed gradually and worsened with time, suggesting that the stimulation may have caused changes in brain function, resulting in a lowering of the seizure threshold. This syndrome is almost identical to the "kindling effect" described by Goddard *et al.* [9] in which progressive changes in brain function caused by repeated electrical stimulation of limbic areas led to the appearance of seizures. These workers concluded however, that the development of seizures was not based simply on threshold reduction, but involved complex reorganization of brain function. Wet-dog shakes are a characteristic of the morphine withdrawal syndrome [27] and it is possible that, given the occurrence of enkephalins in the ACB [11], the shakes observed in the present ACB animals were related to altered enkephalin neurotransmission. Furthermore, it is noteworthy that the application of noradrenaline to the ACB of rats produces a convulsive syndrome [13]. Further work is required to delineate the aetiology of these motor effects.

The behaviour of both groups of rats during self-stimulation was characterised almost exclusively by a locomotor response, evidenced by the shortness of both the initiation and escape latencies. Stimulus-bound behaviours such as sniffing, rearing and exploration, commonly elicited during self-stimulation [14], were notably absent from the ACB animals, and were minimal in the HYP animals. The marked locomotion of the ACB rats is of interest because the ACB is of critical importance in both spontaneous and drug-induced locomotion [1,13]. For example the application of dopamine to this nucleus produces marked locomotor stimulation which is rapid and coordinated. The more bizarre stereotypes such as sniffing, rearing and biting, associated with stimulation of dopamine receptors in the caudate nucleus, are absent [13]. In the present study, the HYP animals displayed a similar behavioural response. Since hypothalamic self-stimulation is generally associated with varied stimulus-bound behaviours, the marked locomotion observed here may be an artefact of the testing procedure.

There is considerable controversy as to why rats terminate self-initiated stimulation. Some workers believe that it is due to an initially rewarding stimulus becoming aversive

[3,18], while others say it is because the reward rapidly diminishes and the rat escapes to have the opportunity of reinitiating the stimulation and renewing the reward [5,25]. We believe the latter effect to be of prime importance in the present study, given the ritualized on-off locomotor behaviour displayed by both groups of animals. Moreover, continuous reinforcement schedules tend to induce a continual ritual of responding [10].

It may be argued that if the stimulation was rewarding, a naive animal would be expected to rapidly learn the response. Although the ACB animals eventually responded just as vigorously as the HYP animals, it took a considerably longer time for this to occur. The difficulty of the task cannot be considered a significant contributing factor here, so we are led to conclude that ACB self-stimulation may be less rewarding than HYP self-stimulation. It is possible that there are changes occurring in the ACB as a result of the stimulation which may be responsible for (or even required for) their eventual vigorous performance. These changes appear to parallel the development of seizures which probably also require complex changes in brain function [9]. Given the importance of dopamine for stereotyped behaviour [22], and the importance of the ACB in locomotor behaviour [1,13], perhaps the postulated changes in ACB function lead to the slow acquisition of a stereotyped ritual, rather than a reward-motivated behaviour. In support of this, chronic ACB self-stimulation has also been reported to produce an enhanced stereotypic response to amphetamine [6] and changes in open field behaviour [14].

If ACB self-stimulation is simply a conditioned locomotor response to a novel stimulus, this may explain the drop-off in initiation performance of the ACB animals over the 25-min test sessions (Table 2), this being a result of fatigue which is not counteracted by rewarding drives as may be the case with the HYP rats. The observation that the ACB rats responded significantly more vigorously after a single day without access to stimulation (Fig. 5) is also consistent with a conditioning hypothesis. In these two situations however, since the escape latency remained fairly constant, the results may also be interpreted as indicating specific changes in the reward value of the stimulation. Such an hypothesis is not inconsistent with the possibility that ACB self-stimulation is less reinforcing than hypothalamic self-stimulation *per se*. Moreover, the data could also indicate that prolonged self-stimulation can become aversive.

It appears that ACB self-stimulation may involve a conditioned stereotyped ritual in addition to the well documented effects of reward, aversion and adaptation. This may be a unique feature of the ACB, or it may be an artefact of the testing procedure since the HYP animals responded in some ways with an essentially similar behaviour. Further experiments are required to determine the relative contribution of each of these factors.

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