CHANGES IN SOCIO-EMOTIONAL BEHAVIOR UNDER IMIPRAMINE TREATMENT IN NORMAL AND AMYGDALO-HYPOTHALAMIC DOGS

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Abstract. The effects of imipramine on learned social responses were examined in ten dogs with dorsomedial amygdalar lesions and/or lateral hypothalamic lesions. Six of the ten dogs were also tested preoperatively. The social responses were instrumentally conditioned using social interaction with the experimenter as reinforcement (petting and verbal reassurance). In the non-lesioned dogs imipramine treatment produced a dose-dependent deterioration of performance during drug administration followed by a long-term amelioration of performance. In the lesioned dogs imipramine produced various changes in performance depending on the pretreatment level of responding. When the pretreatment level of performance was high drug administration resulted in a long-term deterioration, and when performance was poor imipramine produced a continuous and long-term increase. It is suggested that imipramine facilitates the recovery of performance, but suppresses well-performed responses.

INTRODUCTION

Lesions of the dorsomedial amygdala (DMA) or lateral hypothalamus (LH) in dogs lead to hypoactivity, alterations in feeding behavior ranging from hypophagia to aphagia, reduced responsiveness to external

cues and an unwillingness to interact socially with the experimenter (11-13, 29). In our previous paper it was assumed that the deterioration of social instrumental responses (described below) after hypothalamic or amygdalar damage may be due to general decrease in pleasure state (dysphoria, 16). Both DMA and/or LH lesions probably impair brain reward systems, evoking symptoms very similar to human depression: apathy, decreased motility, and a general deterioration of motivated behaviors. This hypothesis is consistent with the widespread concept that depression is produced by a defect in the reward system (7, 32, 34, 37). Although an ideal model of human depression does not exist (see 36 for a review), the amygdalo-hypothalamic syndrome in dogs could win some points for face and construct validity criteria by assessing its usefulness in psychopharmacological research. The most important question is its predictive validity, which can be tested using antidepressants. Since depression is essentially an affective disorder we believe that the dog as an experimental animal has advantages over other species, because emotions are strongly involved in dog's social relations with humans and his emotional expression is easy to understand.

We chose imipramine as an antidepressant drug, because its influence on depressive patients had been extensively investigated (4). The effects of this drug on depressive animals were also most often examined with the various models of depression (31). Also, previous results indicated that imipramine facilitates socially reinforced responses after their impairment by amygdalar lesions (13, 16), and that the general motility and sensori-motor responsiveness in such dogs is increased (14, 15, 23). While in normal dogs, Zagrodzka et al. (38) observed imipramine to produce a decrease in open field locomotor activity, in neurotic dogs it produced an improvement of performance of all tasks tested including socio-emotional responses. Babcock et al. (5) reported an improved performance in dogs with catalepsy under imipramine treatment. Improvement of social disorders induced in monkeys by separation from their mothers was observed by Suomi et al. (35). In the isolated mouse imipramine increased locomotor activity and exploration (20). In normal animals imipramine decreases spontaneous activity, impairs the learning and performance of avoidance responses, and results in symptoms of ataxia (18). Also Kołakowska and Fonberg (21) have shown that imipramine may produce a deterioration of conditioned alimentary-avoidance responses in normal dogs. In normal humans, imipramine does not produce euphoria or elevate mood but rather engenders drowsiness and impairs motor coordination (8, 19). We observed a similar effect in dogs. Fatigability and impaired effective

and cognitive processes are also observed in imipramine treated patients (18). Often these changes are considered as the side effects of imipramine treatment in depressed patients.

From electrophysiological studies it is known that imipramine directly influences the amygdalo-hypothalamic system, potentiating or inhibiting the behavioral responses elicited by electrical stimulation of these structures (3, 27). As demonstrated by Allikmets, Vahing and Lapin (1, 2) imipramine potentiates the serotonine effects in the amygdala while it inhibits cholinergic effects. Such effects are dose-dependent, and large doses have particularly inhibitory properties. Finally, intravenous imipramine has been shown to evoke spike-like EEG patterns in the amygdala (33).

The aim of our present study was to compare the effects of imipramine on socio-emotional behavior in normal and experimentally depressive dogs due to the DMA or LH lesions. We hypothesized, that if the amygdalo-hypothalamic syndrome is a valid model of depression, imipramine treatment should have an ameliorative effect on the disturbed socio-emotional behavior observed in these dogs. We also wished to determine whether the previously observed (11, 12, 29) post-operative deterioration of instrumental social responses (dog-experimenter) were primarily socio-emotional or secondary to disturbed alimentary behavior. Thus unlike previous experiments, the dogs in this study never received food of any type from the experimenters.

METHODS AND PROCEDURES

Experiments were carried out on 10 adult male mongrel dogs weighing 9.5-22.5 kg.

Preoperative training. The dogs were trained to perform five social instrumental responses (CRs). The CRs were considered "social" in that they necessitated the interaction and close physical proximity of the experimenter, and they were reinforced only by the social stimuli of the dog-experimenter interaction, including petting reward and verbal reassurance. The CRs consisted of: sit, paw, sprint, and jump responses, which were performed at the command of the experimenter. After each well-performed response, the experimenter would reward the dog by stroking its head and neck and verbally reassuring it with an accepting tone of voice. The reward period lasted for 5 to 10 seconds. In addition six of the dogs were trained to prostrate themselves ("lie" response). To examine some of the properties of petting reward, during the "lie" response we varied the duration of petting from 5-30 s. In these trials, we recorded the duration the dog remained prostrate

during petting, and also the amount of time the dogs remained pro-
state after petting had been withdrawn. The techniques and recorded
parameters of this training have been described in detail elsewhere (17).

Surgery. After the dogs reached a criterion of ten consecutive
sessions with an over-all level of 90% of the trials correctly completed,
they received electrolytic lesions under Nembutal anesthesia in the
dorsomedial amygdala and/or lateral hypothalamus according to the
stereotaxic coordinates of the Lim, Liu and Moffit atlas (24). The
lesions were performed by passing 3.5 mA of anodal current for three
minutes through stainless steel electrodes coated with enamel except
for 1 mm at the tip. The details of this procedure were described in
previous papers (11, 29).

Imipramine treatment. The procedure for preoperative imipramine
administration which six of the dogs received (Experiment I), was the
same procedure which all 10 of the dogs received post-operatively.
Since we were unable to detect group differences as a function of pre-
operative exposure to imipramine, the postoperative data from all 10
dogs were combined. Imipramine hydrochloride (Polfa) was injected
intramuscularly during 15 consecutive days in the following doses:
25 mg during the first five days, 50 mg during the next five days, and
25 mg during the last five days. The dosage requirements were deter-
mined in previous experiments which did not find a relationship be-
tween the response to imipramine and the dogs body weight (13, 22).
Injections were administered daily at about 9:30 am, and experimental
sessions were conducted on two days of each five-day dose period.
The testing sessions were in the early afternoon (3-4 h after injection),
following the same schedule as that of the training sessions. In order
to test the post-operative effects of imipramine (Experiment 2), the
training sessions were resumed on a weekly schedule ten or eleven
days postoperatively and the imipramine treatment phase began 4-7
weeks later. Training sessions on the same regular basis were continued
for two months after imipramine treatment.

Statistics. A mixed design analysis of variance (25) was used in
order to evaluate the overall effects of imipramine treatment on the
animals performance. Data expressed in percentages were analyzed
after an arcsin $\sqrt{P}$ transformation which corrects the distribution of the
percentages to better estimate the homogeneity of the scores and allows
the use of the analysis of variance technique. The differences in the
data obtained with different imipramine doses in pre- and post-treat-
ment periods were analyzed with the Duncan test (10). The figures
are drafted according to the data analyzed, however, for greater clarity
and relevance to the subsection's subject not all of the data are always
depicted.

General behavioral observations. We recorded all salient changes in the behavior of the dogs: (i) motor coordination and locomotor activity, (ii) emotional responses involving panting and pupillary changes etc., (iii) vocalization (whining, growling, barking).

Histology. Following the testing phase, all animals were deeply anesthetized and perfused intracardially with 10% formal-saline. The brains were removed and stored in 10% formal-saline for several days. Subsequently the brains were sectioned coronally at a thickness of 50 μm with a cryostat, and stained with either Klüver or Nissl method.

RESULTS

Experiment I: Imipramine treatment in normal intact dogs.

General behavior. The distinct changes observed in the behavior of all six dogs under imipramine treatment and after its discontinuation can be divided into two categories.

Motor disturbances. Changes in motor abilities were noted in five dogs. Three of the dogs exhibited disturbances in motor coordination and two others appeared sluggish and slowed locomotion. Overall the dogs seemed to be more susceptible to fatigue and preferred to lie on the floor than remain standing. Some of the dogs showed heavy panting. Four other dogs however, appeared generally excited: they would run around and vigorously explore the laboratory environment.

Emotional or neurotic-like disturbances. During the drug treatment some of the dogs showed increased fear (three dogs), whining (three dogs), and stereotyped movements (one dog). Only one dog (S-11) showed better concentration during the experimental trials than before imipramine treatment.

After discontinuation of imipramine, the remission of the above symptoms was either immediate or progressive. Moreover, an improvement of general behavior was observed after imipramine treatment in comparison to the pre-treatment level. For example, dogs which were reluctant to obey orders before treatment, after the discontinuation of treatment they began to perform willingly and were more active as well. In four of the dogs motor coordination was improved and two dogs were quieter in post-treatment period presumably as results of being less fearful.

Imipramine effects on instrumental performance. During imipramine treatment a decrease in percent of correct responding was observed. However, after discontinuation of the drug, instrumental performance improved surpassing pre-treatment levels. During the treatment not only was there a decrease in the number of correct responses but also the latencies of correct responses were longer (Fig. 1). In some
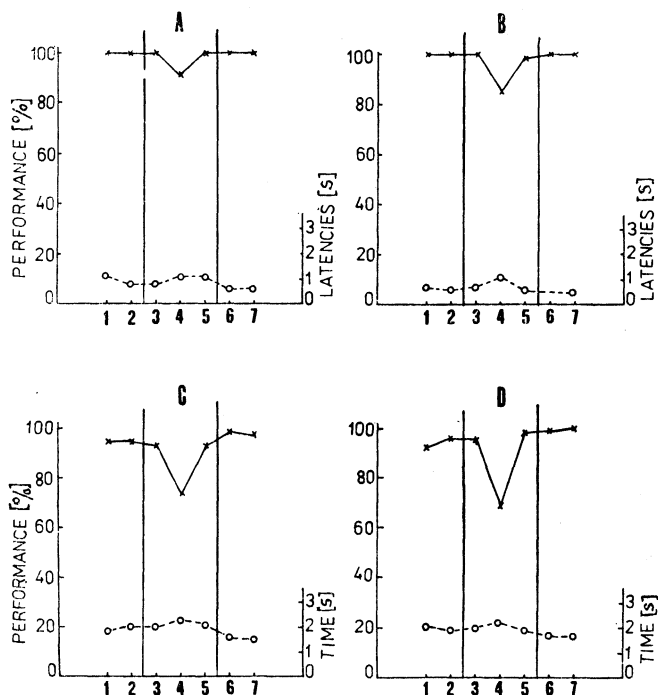
Fig. 1. Influence of imipramine treatment on the mean percentage of correct responses (solid lines) and mean latencies of "sit" and "paw" or durations of "sprint" and "jump" responses (dashed lines) in six normal dogs. Abscissa, successive periods of treatment: before imipramine (1,2), during imipramine (3-5), after imipramine (6,7). Periods of imipramine administration were denoted between two thin vertical lines A, "sit", B, "paw", C, "sprint", D, "jump" responses.

dogs the level of performance of particular tasks remained unchanged or slightly improved, but this was not the case for any one dog on all of the tasks.

Four analyzes of variance performed separately for each response type showed a statistically significant overall effect of imipramine on the latencies of "paw" responses $F(7/35) = 5.23$, $P < 0.001$ and the time of duration of "sprint" $F(7/35) = 8.02$, $P < 0.001$ and "jump" $F(7/35) = 14.27$, $P < 0.001$ responses. At beginning of imipramine treatment (Period 3 in Fig. 1), instrumental performance on all tasks was not significantly affected. The first statistically significant changes occured only later during the treatment in period 4 (Fig. 1), when the imipramine dose was highest: the latencies of the "paw" response and the durations of the "jump" response increased ($P < 0.05$). These responses remained significantly different in Period 5 as well ("paw" — $P < 0.001$, „jump" — $P < 0.01$). Changes in the parameters of the

"sprint" or "sit" responses did not reach significance during any period of the treatment. It is noteworthy, that a comparison of the data from the initial and final treatment periods when imipramine doses were the same (25 mg), did not reveal any significant differences in any of the tasks. Thus the observed deterioration in performance was dose dependent. The greatest decrease in performance was observed when the dose was 50 mg.

Long-term effects of imipramine treatment. The post-treatment period showed a return of performance to or above pre-treatment level. Within the first three post-treatment sessions the level of performance was restored to 100% for "paw" and "sit", and for "sprint" and "jump" the responding exceeded pre-treatment levels. Furthermore, the latencies of "sit" and "paw" responses as well as the durations "sprint" and "jump" tasks became shorter than in the pre-treatment period (Fig. 1). These effects were confirmed by Duncan tests which showed significant differences between the last period of treatment (Period 5) and the two successive post-imipramine periods for "sprint" (Period 6 — $P < 0.05$, Period 7 — $P < 0.01$). A comparison of the "paw" responses was not significant. The post-treatment improvement was immediate and persisted for several weeks till the end of the experiment. Separate analyses at one month post-treatment showed that none of the dogs performed at a level lower than that of the pre-treatment period, and that the response latencies and durations were still shorter in all dogs. Finally, Duncan tests revealed that the comparison of improved performance between Periods 2 and 8 reached the significance of $P < 0.001$ for "paw" and "jump" responses and $P < 0.01$ for the "sprint" response.

Experiment II. Imipramine treatment in amygdalo-hypothalamically lesioned dogs

Anatomy. In three dogs (S-3, S-8, S-9) the amygdala was destroyed only unilaterally but the hypothalamus bilaterally. In four others (S-4, S-5, S-10, S-12) the amygdala was left intact and the lateral hypothalamus was destroyed bilaterally. In the remaining three dogs (S-1, S-11, S-13) bilateral lesions involved both the amygdala and hypothalamus, but the extent of the lesions varied. Lesions involved mainly the dorsomedial part of the amygdala (n. medialis, area anterior) and the lateral part of the hypothalamus. In some cases however, other structures were marginally included (i.e., internal capsule, optic tract, thalamus, hippocampus).

General behavior. The post-operative changes characteristic of amygdalo-hypothalamic dogs were described earlier (11-13, 16, 29), and

consisted of a long-lasting impairment of responses of the socially re-inforced type. The dogs were apathetic, withdrawn and unsocial. At the time post-operative imipramine treatment began performance levels varied between subjects as well as between the various tasks.

Similarly as in Experiment I, behavioral changes under imipramine treatment can be divided into two categories.

Motor disturbances. Alterations in motility were observed in 8 dogs. Among the symptoms, impaired motor coordination apeared in five dogs, and fatigability also in five dogs. In two dogs with decreased motility, sometimes an aimless kind of excitation with locomotion was observed.

Neurotic-like symptoms were noted in five dogs. An increased fear-fulness appeared in four dogs, and apathy or decreased affect in four others. In general the dogs yawned more and showed signs of somno-lence and boredom. In the experimental setting they did not appear motivated. During the intertrial intervals the dogs were often lying on the floor and it was difficult to move them into a preparatory position for the subsequent task. The severity of these changes differed for each dog. For example, S-2 during the pre-treatment phase often jumped over the low barrier competently ("jump" response component), howe-ver, during imipramine treatment he would only step over the barrier. Dog S-5 showed head and body shaking during imipramine treatment. All of these behavioral changes disappeared at various time after the discontinuation of imipramine treatment. General behavior in four of the dogs was clearly improved in comparison with the pre-treatment period. In others this amelioration was more subtle and/or difficult to evaluate behaviorally. In two of the dogs (S-8, S-10) behavioral per-turbations continued. It is difficult, however, to determine whether or not these changes were due imipramine treatment or rather to the development of epileptic seizures observed in dog S-10 3 months and in S-8 4 months post-operatively.

The effect of imipramine treatment on instrumental performance. The effects of imipramine treatment varied in magnitude and direction. In most of the dogs instrumental performance changed, but the same dog might show improved performance in on task and decrements in other tasks. The changes were variable not only between dogs but within individual dogs as well. In spite of impaired coordination and other motor symptoms, only two dogs showed longer durations in the performing the "sprint" and "jump" responses. An analysis of individual data seems to indicate that the magnitude and direction of individual changes due to imipramine depended on the initial (pre-treatment) level of performance. In the lesioned group postoperative performance
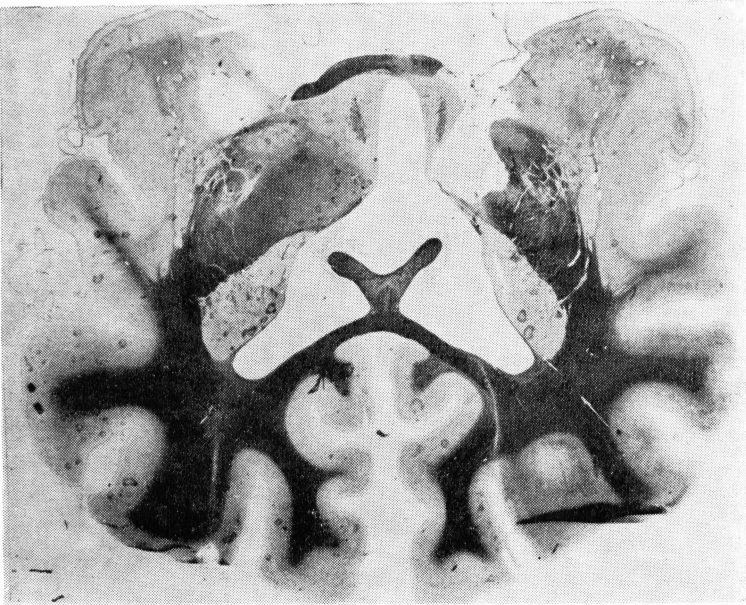
Fig. 2. Presentation of more extensive combined hypothalamo-
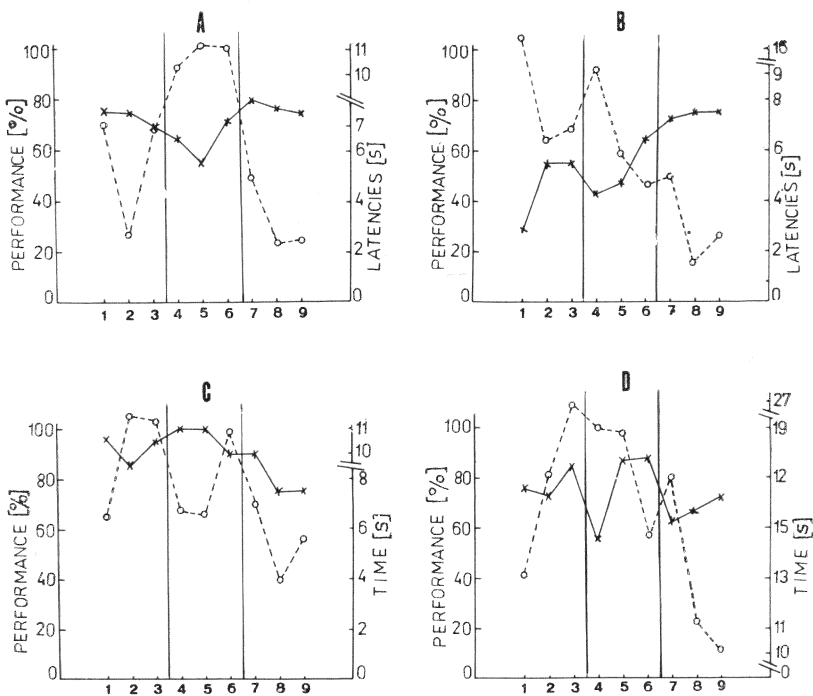amygdalar lesions.

Fig. 3. Influence of imipramine treatment in the more perturbed amygdalo-hypo-thalamic dogs (Group I — mean data for four dogs). Abscissa, successive periods of treatment: before imipramine (1-3), during imipramine (4-6), after imipramine (7-9). Denotations as in Fig. 1.
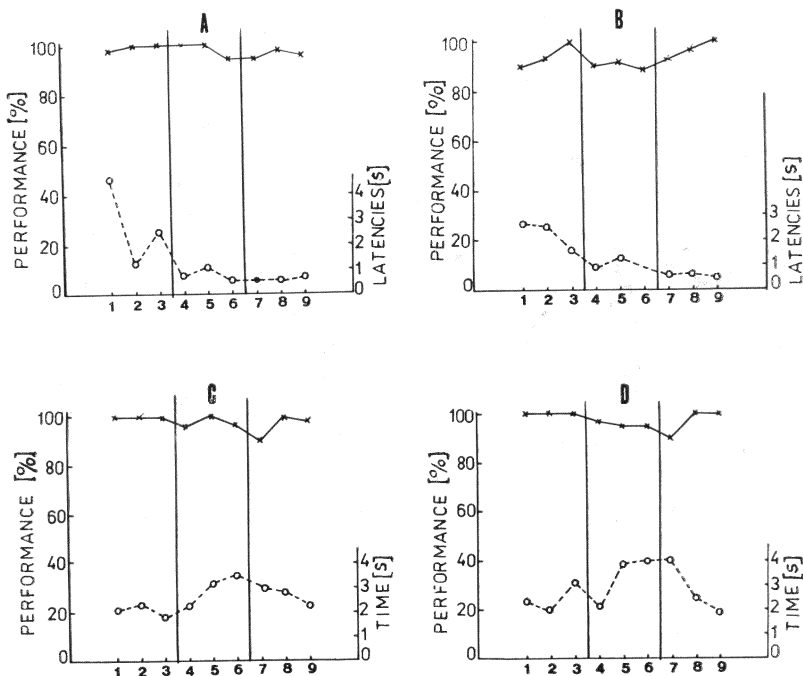

Fig. 4. Influence of the imipramine treatment in the less perturbed amygdalo-hypothalamic dogs (Group II — mean data for six dogs). Denotations in Fig. 2.

baselines varied between and within dogs with respect to different tasks. Using this data the lesioned dogs could clearly be assigned to one of two subgroups according to high or low performance. A 10% decrease in number of correct responses as compared to the preoperative baseline in two of four tasks served as a criterion for assigning a dog to the low performance group (Low Group). Four dogs met this criterion: S-3, S-4, S-5, and S-8. Six other dogs which did not meet this criterion were assigned to a High Group: S-1, S-9, S-10, S-11, S-12, and S-13. It must be noted that some dogs reached the preoperative level of performance although latencies and response durations remained somewhat longer. Thus, even dogs in the High Group differed from normal intact dogs. The appropriateness of our division of the dogs into subgroups was confirmed by the results of four analyzes of variance (Groups X Periods) performed separately for the latencies of the "sit" and "paw" responses and the durations of the "sprint" and "jump" responses. A significant Group effect was found in the latencies of "sit" $F(1/63) = 15.72$, $P < 0.001$ and "paw" $F(1/63) = 6.05$, $P < 0.05$ responses; as well as in the durations of "sprint" $F(1/72) = 22.66$, $P < 0.005$ and "jump" $F(1/72) = 68.13$, $P < 0.001$ responses. Between group differences were found not only in the mean latencies and mean durations of the performed tasks, but also in different responsiveness to the imipramine treatment. Interactions between Groups and Periods were significant for the "sit" $F(9/89) = 3.26$, $P < 0.005$, "sprint" $F(9/99) = 2.25$, $P < 0.05$, and "jump" $F(9/99) = 3.83$, $p < 0.001$ responses. Only the interaction for Groups and Periods for the "paw" response did not reach significance. The analysis of these two subgroups data demonstrated that dogs with a low pre-treatment level showed improved performance in terms of percent correct responses, latencies and durations, whereas dogs of the High Group showed decreased performance in these parameters (Fig. 3). This deterioration of the High Group was slight and not dose-dependent (Fig. 4) Individual analyses for the latencies of the "sit" and "paw" responses and for the durations of the "sprint" and "jump" responses did not reveal statistically significant differences.

The dogs of the Low Group were more affected by imipramine administration, but the direction of the behavioral changes differed in the individual dogs with respect to each task. In the "sit" response, correct responding for the entire group decline by 7% for the whole period of imipramine administration, and the latencies of this response were increased as well (Fig. 3A). An analysis of variance $F(9/18) = 3.00$, $P < 0.05$ and the Duncan test revealed significant differences in latencies between the first period of the pre-treatment phase (Period 1) and the last treatment period (Period 6) $P < 0.05$, and between Period 2 of

the pre-treatment phase and Periods 5 and 6 during imipramine treatment: $P < 0.05$ and $P < 0.01$ respectively. The mean percentage of correct responses for "paw" was not different from that of the pre-treatment period, but the level of performance was fluctuating and decreased distinctly at the beginning of treatment (see Fig. 3B), and the latencies of the "paw" response decreased, but neither of these trends reached statistical significance.

Under imipramine the mean percent of correct responses for "sprint" and "jump" increased 1% and 3% respectively. Decreases in response durations (Fig. 3C, 3D) did not reach statistical significance. The percentage of correct "paw", "sit", and "jump" responses decreased markedly at the beginning of the treatment (Periods 4 and 5), but in the last treatment period performance improved. The latency of the "sit" response continuously increased and the latency of the "paw"
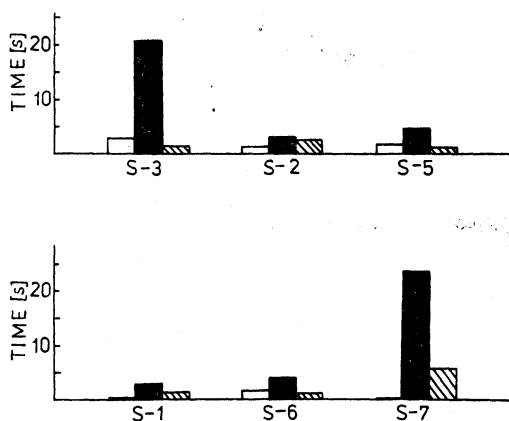

Fig. 5. Mean time of lying without petting reward in the individual dogs: before imipramine (open bars), during imipramine (black bars), after imipramine (crossed bars). Note that only the first 60 s of lying was recorded, then the trial was terminated.

response decreased. The "sprint" response was clearly improved in the first period of drug administration (Period 4) in terms of duration and percent correct, but showed a slight deterioration at the end of Period 6. In all six dogs trained in the "lie" response the amount of time spent lying increased substantially during imipramine treatment (Fig. 5). It should be pointed out that after 60 s of lying without petting reward the trial was terminated, therefore Fig. 5 does not reflect the full extent of this increase which tended to be much longer.

The effects of imipramine during the post-treatment period. Dogs

which had began with a higher level of responding performed poorly in the first post-treatment. The number of successfully completed responses decreased and latencies and durations increased. During the subsequent experimental sessions their performance improved, but the latency and duration differences on all the tasks in the post-treatment period were not statistically significant. In contrast the dogs which began with lower baselines showed improved performance after imipramine was discontinued. Particularly, the latencies and durations shortened and did not fluctuate as much as in the pre-treatment period. This effect was stable; one month after discontinuation of imipramine the performance of these dogs was even better than in the early post-treatment period (Fig. 6).
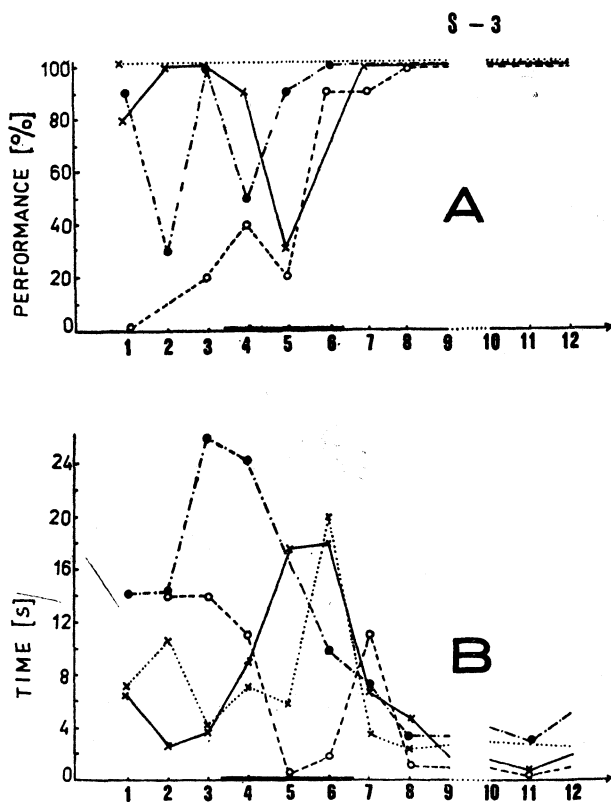

Fig. 6. Influence of imipramine treatment on the percentage of correct responses (A) and latencies of "sit" and "paw" and durations of "sprint" and "jump" responses (B) in the dog S-3, Abscissa, before imipramine (1-3), during imipramine (4-6), after imipramine (7-9) and one month after imipramine (10-12). Sit, solid lines; paw, dashed lines; sprint, dotted lines; jump, dash-point lines.

DISCUSSION

The results of the present experiments show that imipramine treatment has an impact on the behavior of normal and amygdalo-hypothalamic dogs. The results obtained in normal dogs are consistent with the current literature regarding the effects of imipramine treatment on normal subjects. They support the previous results of decreased motor activity (13, 21, 23, 38). However, it is not completely clear why all of the conditioned responses did not decrease in a similar fashion. Some inter-task differences can be explained by locomotor disorders, and the fatigability of the dogs. Such side effects of imipramine treatment were noted by other authors (8, 19), and could have particularly influenced the "sprint" and "jump" responses which required energetic motor sequences. It is noteworthy that apparently paradoxical behaviors were occasionally seen in some of the dogs. For example, some dogs seemed to be highly aroused as measured by aimless locomotor activity yet on close examination their appearance was one of drowsiness. Electrophysiological studies have demonstrated that low doses of imipramine increase the excitability of the subcortical arousal system while simultaneously producing a slowing of cortical electrical activity which is resistant to desynchronization (30). It seems that the undirected excitation observed in our dogs could be explained by the non-specific excitatory actions of imipramine which simultaneously inhibit purposeful, goal oriented behaviors as well as the performance of conditioned instrumental responses. The higher doses of imipramine produced more severe decrements in instrumental responding, and resulted in pronounced drowsiness and greater locomotor disturbances. Such results are consistent with clinical observations (8) and other data from animal experiments. For example, Steiner and Himvich (33) found that under high imipramine doses (3-10 mg/kg) rabbits were unresponsive to peripheral stimulation such as noise, touch, or pain. In the experiments of Rubio-Chevannier (30) higher doses of imipramine inhibited even the excitability of structures which were usually excited by low doses. An unexpected result was the stable, long-term ameliorative effect of imipramine in normal dogs. Although this result could be due to overtraining, the dissappearance of neurotic-like symptoms suggests a beneficial effect of imipramine. Similar results were reported previously (11, 38).

Our results concerning imipramine treatment in amygdalo-hypothalamic dogs are less clear due to the great variability of responsiness

to treatment. Factors that account for the variance could include the different levels of performance before the treatment, differences in lesion character and magnitude and differences in body weight; the group in Experiment II had a greater range body weights (9.5-22.5 kg) than that of Experiment I (15.5-22.5 kg). Although we did not detect a group effect for pre-operative imipramine treatment, the fact that some of the dogs had already been exposed to imipramine could have contributed to the variance in Experiment II. Analyzes of the individual data did not reveal any consistent relationship between the direction of these changes resulting form imipramine treatment and any one of these factors. We point them since they may have affected physiological variables in subtle and unanticipated ways. For example, Korczyński and Fonberg (22) have found that a second treatment of imipramine had a greater parasympatholytic effect on salivation than the first exposure to' the drug. However, we believe that the above factors were not essential since the level of task performance often varied within subjects. This last finding is of considerable importance and suggests that similarly rewarded instrumental responses may be learned and sustained by different mechanisms in the same subject. Consequently, such responses can be affected in quite different ways by the same physico-chemical changes induced by a lesion or treatment. In this light, it would be potentially misleading to interpret within group differences in terms of the prevalence of cholinergic or noradrenergic function associated with the various lesions. A recently proposed cholinergic-monaminergic theory of affective disorders (9), emphasizes both the dysfunction of homeostatic mechanisms essential to the maintenance of balance between neurotransmitter systems, and the cholinergic-monaminergic imbalance; rather than simply the under or over-function of either transmitter system. Analysis of our results indicated that similar to normal dogs, the less disturbed amygdalo-hypothalamic dogs showed impaired instrumental performance during imipramine treatment but not in a dose-dependent manner. The long-term (post-treatment) consequences of imipramine, although beneficial for normal group were not necessarily the same for the operated dogs. While any changes in the post-treatment period were positive in the non-lesioned group (Experiment I), the post-treatment performance in the lesioned was variable. Poldinger (28) reported that the action of imipramine is slower in patients than in healthy subjects. This observation could perhaps explain the lack of dose-dependent effects and the fact that the less disturbed amygdalo-hypothalamic dogs did not immediately return to the pre-treatment baseline of performance.

Contrariwise, the more post-operatively perturbed amygdalo-hypo-thalamic dogs improved their performance during the imipramine treatment. Their performance was more stable with the continuation of training and persisted after imipramine was withdrawn. We did not find a gradual decline in the post-treatment benefits of imipramine, as did Suomi et al. (35). This difference suggest that imipramine acts specifically on inhibited instrumental (i.e., motor) responses. Such an interpretation is compatible with clinical findings which attest to the particular usefulness of this drug in cases of endogenous depression with inhibition (4), and the report of Babcock (5) on its anticataleptic effects. Although our results coroborate the role of imipramine in facilitating the recovery of inhibited response, they do not speak for its general antidepressant action. Parallel findings have been reported by others, in the reward-reduction model using self-stimulating rats, imipramine does not have the predicted "antidepressant" action (6), and earlier studies acknowledge that antidepressants rarely increase the rate of self-stimulation and in large doses they may depress it (32, 34). Finally, tricyclic antidepressants do not directly ameliorate the behavior of reserpine treated mice (26). The main question, as to what are the neurochemical and behavioral conditions in which imipramine is effective, is difficult to answer since imipramine alters a number of transmitter systems (E, NE, DA, 5-HT) which are impaired to varying degrees in this experimental model of depression. It seems reasonable to speculate that after a partial loss of the amygdalo-hypothalamic regions known to be involved in motivation, imipramine potentiates the activity of auxilliary structures of partially redundant function. It is thus possible that the first sites of imipramine action are the hypothalamus and amygdala, the excitation of which results in behavioral inhibition, mediated possibly by serotonin. Whereas, in the amygdalotomized subject, imipramine acting through different transmitter systems (e.g., catecholamines) could have quite opposite excitatory effects. It seems that the anticholinergic action of imipramine which possibly results in mania-like symptoms (as in locomotor stereotypies reported above), bypasses the amygdalo-hypothalamic regions destroyed in these experiments while its inhibitory effect on the preserved lateral part of the amygdala could contribute to such symptoms.

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