ELECTROMYOGRAPHIC ASSESSMENT OF SPINAL REFLEXES IN EXPERIMENTALLY DEPRESSED DOGS TREATED WITH ANTIDEPRESSANTS

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Abstract. In seven mongrel dogs the syndrome of depression was evoked by bilateral electrolytic lesions in lateral hypothalamus and/or dorsomedial amygdala. The effects of tricyclic antidepressants on general mood, spinal reflexes recorded by electromyographic method, and heart rate were tested. The reactivity to most external stimuli was increased and general depression was slightly reduced.

INTRODUCTION

In our previous papers it was described that bilateral lesions in the dorsomedial amygdala and/or lateral hypothalamus in dogs produced a syndrome of depression which, apart from afagia and adipsia, produced also such symptoms as apathy, hypodynamia, hypokinesia, decrease of reactivity to external stimuli, changes in posture and tendency to cataleptic-like positions (7–10, 12, 31).

The problem arises whether observed by us previously symptoms of depression are caused by motivational changes, or, at least partly, by changes in the motor system which secondarily may produce a decrease of both general activity and instrumental performance as well as to influence the general mood. In order to examine the latter possibility we investigated spinal reflexes and various aspects of motor activity in lesioned dogs with and without antidepressant treatment. Our preliminary study has shown that antidepressants produced diminution of depression in dogs with hypothalamic and amygdalar le-
sions (14). On the other hand in view of our data from the other series of experiments on similar problems it was interesting to investigate the effect of antidepressants also on the motor component of depressive syndrome.

The early effects of antidepressive tricyclic drugs therapy in humans consist in psychomotor activation, and the amelioration of the mood follows later. One of the methods to measure experimentally the increase of psychomotor arousal is to check the neurological spinal reflexes, and in particular the responsiveness to the various external stimuli. Investigations of sensorimotor changes in rats and cats with motivational disturbances as result of CNS lesions become recently the subject of great interest and are investigated also by other authors on cats and rats (26, 35, 37).

The reactivity of spinal neurons is directly controlled by the reticular formation (24, 25). In addition their activity is modulated by the other mesencephalic structures (30) as well as telencephalon and in particular by amygdala (1, 15). Stimulation of the amygdala may either excite or inhibit the spinal reflexes, for example knee jerk (17). On the other hand antidepressants may activate the amygdalar neurons (3, 4, 18, 38) and in this way act directly on motivation.

The purpose of the present paper was to study the effect of treatment by tricyclic antidepressants on the sensorimotor activity of the dogs in order to evaluate the role of the excitation of this system in the reduction of depressive states.

METHODS

*Animals.* Experiment was performed on 7 adult male mongrel dogs. The dogs for this experiment were chosen from a large group of dogs with extensive lesions of hypothalamus or amygdala. The criterion used to choose these dogs from the larger group was the presence of obvious symptoms of depression and not the dimensions of lesions which were different in particular dogs. In dogs My 1 and My 2 dorsomedial amygdala was damaged, in dogs My 3, My 4 and My 5 — lateral hypothalamus and amygdala, and in dogs My 6 and My 7 — lateral hypothalamus.

*Electromyographic technique,* according to Lindsley et al. (25) can be used as an appropriate index of limb muscle activity. The examined reflex activity was assessed during series of neurological tests. The electrical activity of muscles was recorded on the Mingograf through the surface electrodes which were adhered with collodion to shaved skin above the following muscles: m. tibialis anterior, m. gastrocnemius
and m. sartorius. The dogs were placed in a special hammock which prevented dislocation of the animal, but allowed movements of all four extremities. After a few days of preliminary adaptation, the experiment started. The following reflexes were tested: reflexes evoked by tactile stimuli (strokes with a small brush), nociceptive stimuli (pinching with fine tweezers) and pressure stimuli, (pressing with fingers). Classification of stimuli was used as in Afelt's experiment (2). The stimuli were applied to various points on the left hind limb, and EMG activity was recorded from the same limb. To evaluate general reactivity EMGs were also recorded while the fore or contralateral hind limb was stimulated. An air-puff into the ear was used as a strong aversive stimulus.

After an initial period of habituation to the experimental situation, the experimental sessions were performed 5 times a week. In session which lasted about 20 min a random schedule of stimuli was used. The level of sensorimotor responsiveness was scaled into four score categories, taking into account both the duration and the amplitude of EMG records. The following score categories were used: no response — 0, weak response — 1, moderate response — 2 and strong response — 3. The mean values of scores for responses to different kinds of stimuli were calculated from five successive experimental sessions.

To evaluate the emotional state of animals the heart rate was recorded with electrodes placed on the chest above the heart and near the ankle of the hind right limb. The heart rate was calculated for 30 s before and after each experimental session period. In addition observations of general motility in every day situations and emotional relations to experimenter were made every day.

**Antidepressant treatment.** Antidepressive tricyclic drugs had been injected intramuscularly 2 h before experimental session during a period of 3 wk, in doses which according to our preliminary data produced a sufficient effect. During the first and third week doses of imipramine were 2.3 mg/kg and during the second week 4.6 mg/kg. Amitriptyline was injected in increasing doses, namely, during the first week 0.9 mg/kg, in the second week 2.3 mg/kg and in the third week 4.6 mg/kg. In two dogs (My 5 and My 7) the imipramine treatment was repeated in a similar way after interval of several weeks.

**RESULTS**

In the dog on which observations were performed before and after the operation, the prominent postoperative decrease of both sensorimotor responsiveness (decrease of spinal reflexes) and general reacti-
veness was observed (Figs. 1 and 2). Similar low reactiveness was observed in dogs with LH lesions and those with both LH and DMA lesions.

Antidepressant treatment augmented, as a rule, the EMG responses to various stimuli (Table I, Fig. 1). This increase was particularly pronounced in the tests of general reactiveness, during which the fore and

![Fig. 1. Examples of EMG records of reflex muscle activity evoked by tactile stimulation in dog My 7. Records were taken before (A), after lateral hypothalamic lesions (B), during imipramine (C), and after imipramine treatment (D). 1, time in seconds; 2, heart rate; 3-5, EMG records of m. sartorius, m. tibialis anterior and m. gastrocnemius, respectively. The vertical bars on all channels of records were obtained by standard hand-marker of Minograf and correspond to the moments of stimulus application.](image-url)
contralateral hind limb were stimulated. Such stimulation evoked a greater activity of muscles of the left hind limb than before drug treatment. For example, in dog My 7, responses to tactile stimulation of either fore limb or to air-puffs to the ear reliably produced greater responses in the hind leg. These results were the most evident during

Fig. 2. The reflex muscle activity and heart rate in dog My 7 before and after lateral hypothalamus lesion. After operation the animal was given imipramine in two series (upper and lower part). Each block represents the mean value of 5 consecutive sessions. Note the decrease of reflex muscle activity after LH lesion and the increase after the first week of the second treatment. The mean heart rate was calculated for the period before (first half of black column) and after (the second half) the experimental session and is given in percentage in relation to the first preoperative block. 1, touch reflexes; 2, pressure reflexes; 3, pain reflexes; 4, general reactiveness; 5, heart rate.
The comparison of antidepressant treatment in particular dogs in respect to reflex EMG responses and heart rate. Direction of arrow shows decrease (↓) or increase (↑) of mean EMG responses. Range of changes for EMG responses: dash (<25%), one arrow (25%–50%), two arrows (51%–100%), three arrows (> 100%); for heart rate; (10%–20%), (21%–30%), (> 30%), respectively, cross—lack of data. AMT, amitriptyline; IMP, imipramine; A, touch reflexes; B, pressure reflexes; C, pain reflexes; D, general reactivity; a, heart rate before and b, after experimental session

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repetition of imipramine treatment (Fig. 2). For the other reflexes the effects of imipramine treatment varied in individual dogs. While in one dog, My 5 the general reactivity and responses only to pressure stimuli increased (Fig. 3), in another, dog My 3, only the reactivity to pain stimuli increased (Fig. 4).

When higher doses of imipramine were used (e.g. 4.5 mg/kg) the decrease in reactivity was sometimes observed (see dog My 3 in Fig. 4). Also heart rate measured before and after the experimental session was influenced in a different manner by antidepressant treatment, but varied in individual dogs. However, as a general rule, when reflex reactivity was increased, heart rate during the same stimuli also increased. In some cases (as e.g., dog My 3), the frequency of heart rate was even three times greater during antidepressant treatment than before and such an increase sometimes lasted for several seconds after stimulation. Such extensive and prolonged increase in heart rate was never observed before the drug treatment.

When drug treatment was discontinued, the drug related effects subsided gradually, sometimes with an increase of reactivity in the immediate post-treatment period. In one case (dog My 7), an increase of reactivity was observed throughout the whole post-treatment period, lasting 2 wk. The first treatment with imipramine seems to be less effective than the repeated one.

During antidepressant treatment various changes were also observed
in general behavior. The dogs were more aroused, spent less time standing in one position, were more dexterous in movements and they more easily let the experimenter to lead them to walk. They seemed to be more interested in their surroundings and more reactive to ex-

Fig. 3. The effect of imipramine administration on reflex muscle activity and heart rate in dog My 5 after LH and LA lesions. General reactiveness represents reflex muscle activity evoked by stimuli applied to parts of the body other than the limb from which the EMG was recorded. Denotations as in Fig. 2.

ternal stimuli. Their attitude toward humans also slightly changed, in particular toward the well known experimenter. Instead of being indifferent (which was a typical effect of operation) they were more hostile and aggressive and less submissive than before treatment (10, 11).
Administration of tricyclic antidepressants to a dog depressed in result of medial amygdalar and lateral hypothalamic lesions, increased the responsiveness of these dogs to external stimuli and also increased their general motility. On the other hand, the ameliorating effect of antidepressants on general mood was much weaker than that of the lateral amygdalar lesions on depression produced by either dorsomedial amygdalar or lateral hypothalamic damage (7, 9, 10). Similarly, the effects of antidepressants on the instrumental responses of LH and DMA dogs were much smaller than LA lesions (in preparation).

It is well known that the amygdala and hypothalamus are active neurochemically and that there are areas in which either terminate or pass through the adrenergic, cholinergic, serotonergic and dopaminergic pathways (17). Dorsomedial part of the amygdala, as it was shown by Hall (16), are adrenergic (detected by high monoaminoxydase activity), whereas basolateral amygdala shows a high level of acetylcholinesterase activity (27, 28). Therefore lesions of DMA and LA may act antagonistically on neurochemical mechanisms.
After amygdalar lesions the cholinergic-adrenergic balance may be disturbed. Medial amygdalar lesions may produce a prevalence of the cholinergic system. Lesions of LA subsequent to DMA restoring the normal cholinergic-adrenergic balance lead to a restoration of normal behavior (9, 10). On intact subject in which depression is produced by a low level of monoamines or their disturbed metabolism, the antidepressive drugs help to restore this balance by acting on amygdalar neurons (possibly in the dorsomedial amygdala). Similar neurochemical balance may be detected between ventromedial and lateral hypothalamus (29, 32).

After an extensive destruction of dorsomedial amygdala (as well as damage of the hypothalamus which is also involved in adrenergic mechanisms (32)), there may be no basis for such improvement and the full effects of the drugs cannot be shown. Our present experiments were performed on dogs, most of which sustained both hypothalamic and amygdalar lesions.

It is known that antidepressants activate the amygdaloid complex. For example, it was observed that imipramine injections produced decrease of the threshold for afterdischarges and prolonged the duration of amygdaloid neurons discharges (18, 33, 38). On the other hand a decrease of afterdischarges when they were evoked by electrical stimulation of the amygdala was also described (20). Experiments of Allikmets and Lapin (4) and Allikmets (3), indicate that the amygdala is the structure particularly sensitive to antidepressive drugs and that lesions of this structure change the emotional responses to administration of either cholinergic or adrenergic agents in the rats.

In the absence of amygdalar or hypothalamic structures most neurons receptive for the action of antidepressants are probably destroyed and therefore the ameliorating effect of antidepressive treatment may be less effective than in intact subjects. On the other hand, the amygdalar damage may also influence the spinal reflexes as such (19). Similarly hypothalamic damage may produce deterioration of spinal reflexes. As it was shown by Wayner (36) stimulation of lateral hypothalamus facilitates the spinal motoneurons.

In the present experiment the effect of tricyclic antidepressants was much greater on the sensorimotor reactivity than on the motivational depression and social relations with experimenter. In some dogs we even observed a triple increase of responses after drug injections as compared with these responses before treatment.

This effect might be also partially evoked by a direct influence of imipramine on the spinal apparatus. It has been shown that catecholaminergic descending pathways project to the both sensory (e.g., sub-
stantia gelatinosa) and motor (ventral horn) systems of the spinal cord (6). Imipramine which is assumed to increase the monoamine level by their reuptake inhibition (21) and to mimic or potentiate the sympato-mimetic effect of catecholamine (5), may cause an augmentation of sensorimotor reactivity at the spinal cord level. Imipramine may also improve the state of muscles, increasing and prolonging their reactivity, thus preventing exhaustion (34). Taking under consideration the above cited data and our present results, it may be presumed that the excitatory effect of imipramine on the spinal cord might be more effective if the modulatory influences from the higher levels of CNS are changed in the result of the damage of amygdala and/or hypothalamus.

Also increase of heart rate used by us as an additional test reveals the excitatory effect of treatment. It should, however, be taken into account that although tricyclic antidepressants, because of their anticholinergic and cardiotoxic action, may influence the heart rate. We observed in another series of experiments (in preparation) that in normal dogs imipramine in the same doses produced as a rule a decrease of normal heart rate. In lesioned dogs, in which heart rate is lower than before operation, imipramine produced its increase.

The effect of antidepressive treatment on motivational changes was rather small. Dogs did not regain their positive attitude toward the experimenter; on the contrary, their increased reactiveness was mostly revealed by aggressiveness and hostility. This fact is in agreement with Allikmets' (3) findings that antidepressants produced increased aggressiveness in amygdalar rats.

Another problem to discuss is a great individual variability to the imipramine treatment. One factor not completely understood is the differences between genuine individual characteristics of the dog. We know that antidepressive treatment in normal dogs also does not produce identical effect in particular subjects (13, 22, 23). This problem, however, needs further investigations. In lesioned dogs an additional factor influencing the individual variability was caused by the fact that lesions were different in each particular dog. In this paper we choose the subjects according to behavioral symptoms of depression and not to the size of damage. Therefore, an unequal damage of adrenergic—cholinergic system may in a different extent impair the adrenergic substratum for adreno-mimetic effects of imipramine action.

At present it is difficult to draw definite conclusions and we plan now to damage selectively either the medial amygdala or the lateral hypothalamus in order to elucidate the role of these two structures in above discussed aspects of the mechanisms of various depressive
symptoms. Our method in evaluating sensorimotor changes is precur-
sory in this field. For this reason, and because of the lack of compa-
rable data of other authors, it has the shortcomings characteristic to
works of that kind. However, the general trend, i.e., the increase of
sensorimotor activation as the effect of antidepressive drug treatment
is obvious and in that respect this work fulfill our aim.

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