COMPARATIVE STUDIES ON THE EEG EFFECTS OF IMIPRAMINE AND CHLORPROMAZINE IN THE NORMAL AND RESERPINIZED RABBITS

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Among a series of clinically available psychopharmacological agents chlorpromazine is known to be effective against the reactive or neurotic depressive disorders with little effect on the endogenous depression, while imipramine is described to be very effective against the endogenous disorders by activating the psychic processes rather than by sedating. Therefore, the comparison of the pharmacological effects of both agents has been a matter of much concern. Domenjoz and Theobald (1) have found little difference in the anti-acetylcholine, anti-barium chloride and anti-serotonin potencies between imipramine and chlorpromazine using the isolated small intestine. However, relative anti-histamine potency appeared to depend upon the experimental preparations used. Chlorpromazine proved more potent against histamine on the isolated ileum, while imipramine was more potent in antagonizing the effects of histamine on the ear vessels of rabbits. Sigg (2) has reported that both agents prolong the barbiturate sleep and alcohol sedation and depress the motor activity in mice and the conditioned avoidance response in rats, though chlorpromazine is more potent than imipramine in all respects. Further, he has shown the difference between both agents in the peripheral effects; imipramine potentiates the contractile responses of the nictitating membrane of cats to stimulation of the cervical sympathetic nerve and to exogenously administered noradrenaline or serotonin, but chlorpromazine suppresses either response. He has also described the divergency in the effects of both agents on the pressor responses of dogs to noradrenaline. Thoenen et al. (3,4) have shown the potentiating effect of imipramine on the contractile response and noradrenaline output of the isolated perfused spleen of cats to sympathetic stimulation, in contrast to the suppressing effect of chlorpromazine.

Axelrod et al. (5,6) have demonstrated that imipramine inhibits the uptake of tritiated noradrenaline in the brain of intact rats, while chlorpromazine does not. It is well known that the effects of imipramine and chlorpromazine on the spontaneous EEG coincide well; both agents produce the resting pattern intermingled with the spindle bursts.
The depletion of monoamines in the brain by reserpine has widely been demonstrated in association with the simultaneous development of sedation. The antagonistic effect of imipramine against the depressed behavior caused by reserpine in the experimental animals has also been discussed in relation with the role of endogenous monoamines in the central nervous system.

In the present experiments, the effects of imipramine and chlorpromazine on the cortical and hippocampal EEG were comparatively studied in the intact and reserpinized rabbits.

METHODS

Sixty-two male albino rabbits weighing 2 to 3 kg were used. After the insertion of tracheal cannula, the head of animals was fixed on the stereotaxic instrument of Todai Noken type under ether anesthesia. The EEG in the motor cortex was recorded epidurally by means of a monopolar silver ball electrode at the site, 2 mm lateral from the sagittal suture and 2 mm frontal from the coronary suture. The indifferent electrode was placed on the frontal bone of the ipsilateral side. The hippocampal EEG (P: 6, L: 6, H: 5) was recorded using a silver needle electrode insulated except the tip.

The recruiting response was obtained by electrical stimulation of the centre médian nucleus of thalamus (P: 5, L: 2, H: −1) for 6 seconds with square waves, 8 cps, 1 msec in duration and 0.5 to 5 volts in intensity. The reticular arousal response was also obtained by stimulation of the brainstem reticular formation (P: 9, L: 2, H: −2) for 6 seconds with square waves, 200 cps, 1 msec in duration and 0.3 to 3 volts in intensity. The stimulation electrode was a pair of dental broaches insulated except the tip and 2 mm apart from each other. The stimulation thresholds for both recruiting and reticular arousal responses were compared before and after the drug administration. The coordinates of the subcortical structures were determined according to the topographic map of Sawyer et al. (7). The experiments were started at least 2 hours after the termination of the surgical procedures and ether inhalation at the room temperature of about 24°C.

Imipramine in the doses of 0.2 to 20 mg/kg and chlorpromazine in the doses of 1 to 10 mg/kg were injected into the marginal ear vein in the intact or reserpinized rabbits. The reserpinization was carried out with the intraperitoneal injection of 1 mg/kg of reserpine about 24 hours before the surgical procedures.

RESULTS

1. Spontaneous EEG in the restrained rabbits

The spontaneous EEG in the restrained rabbits was classified into 6 groups according to the regularity, voltage and frequency of the EEG in the motor cortex, as shown in Fig. 1. The cortical EEG in the I and II groups consisted of the resting pattern; the irregular high-voltage (100–300 μV) slow (1–2 cps) waves. The EEG in the II group was usually intermingled with the spindle bursts, 10 to 12 cps and 200 to 300 μV, while the EEG in the I group was not mixed with the spindle bursts. The hippocampal EEG in the I and
II groups was also the irregular high-voltage (400-600 μV) slow (1-2 cps) waves and that in the II group was mixed with low-voltage (20-60 μV) medium (7-14 cps) waves.

The cortical EEG in the V and VI groups showed the alert pattern; the low-voltage (20-60 μV) fast (20-30 cps) waves. The hippocampal EEG in these groups was regular waves, 100 to 200 μV and 4 to 6 cps. The cortical EEG in the V group was also mixed with the low-voltage (50-100 μV) slow (4-6 cps) waves synchronized with the hippocampal regular pattern.

The cortical EEG in the III and IV groups consisted of the mixed pattern; the high to medium-voltage and slow to medium waves. The EEG in the IV group was inter-
mingled with the sporadic low-voltage fast waves, while that in the III group was not mixed with the sporadic low-voltage fast waves.

2. Effects of imipramine on the spontaneous EEG in the intact rabbits

In about half of the experimental animals, 0.2 mg/kg of imipramine produced a manifestation of the alert pattern in the cortical and hippocampal EEG (Fig. 2). However, the intravenous injection of 2 mg/kg of imipramine resulted in the resting and mixed patterns of the EEG associated with the behavioral sedation in 10 out of 12 animals. The increase in the doses to 7 mg/kg produced the manifestation of the resting pattern (the I and II groups) in all animals, as shown in Table 1. One rabbit showed a dissociation

![Fig. 2. Effect of imipramine on the spontaneous EEG of the non-treated and reserpinized rabbits. Calibration: Ordinate 100 µV, abscissa 1 second.](image)

<table>
<thead>
<tr>
<th>Types</th>
<th>Doses (mg/kg)</th>
<th>Non-treated animals</th>
<th>Reserpinized animals</th>
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* : Number of animals
between the cortical and hippocampal EEG by the administration of 7 mg/kg of imipramine; the cortical EEG turned to the resting pattern but the hippocampal one showed the alert pattern.

The intravenous injection of imipramine above 10 mg/kg sometimes killed the animals without manifesting the seizure discharges in the cortical and hippocampal EEG.

3. Effects of chlorpromazine on the spontaneous EEG in the intact rabbits

The intravenous injection of 1 mg/kg of chlorpromazine resulted in the resting pattern (the I, II and III groups) associated with the behavioral sedation in 14 out of 15 animals, as shown in Fig. 3 and Table 2. The further increase in the dose up to 5 mg/kg, however, did not progress the EEG change. A few animals, whose spontaneous EEG

![Diagram of EEG changes](image)

Fig. 3. Effect of chlorpromazine on the spontaneous EEG of the non-treated and reserpinized rabbits.

Calibration: Ordinate 100 μV, abscissa 1 second.

**Table 2.** Effect of chlorpromazine on the spontaneous EEG of the non-treated and reserpinized rabbits.

<table>
<thead>
<tr>
<th>Types</th>
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<th>Reserpinized animals</th>
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*: Number of animals
belonged to the V and VI groups before the drug administration, responded to the doses of chlorpromazine with the resting pattern in the cortical EEG but with the unchanged manifestation of the alert pattern in the hippocampal EEG. The dissociation between the cortical and hippocampal EEG was usually observed within 30 minutes after the drug administration.

4. Effects of reserpinization on the spontaneous EEG

At about 24 hours after the intraperitoneal injection of 1 mg/kg of reserpine, most of the animals showed miosis, ptosis, sedation and diarrhea. The spontaneous EEG in more than 3/4 of the reserpinized animals showed the resting and mixed patterns (II to IV group), as summarized in Tables 1 and 2. The more stabilized manifestation of the resting pattern in the reserpinized animals than the intact ones was demonstrated by the less responsibility to external stimuli and the earlier reversibility of the alert pattern to the previous level. No dissociation between the cortical and hippocampal EEG was observed in the reserpinized animals.

5. Effects of imipramine on the spontaneous EEG in the reserpinized rabbits

The intravenous injection of 0.2 mg/kg of imipramine produced the alert pattern in more than half of the reserpinized animals, whose spontaneous EEG was mainly the resting pattern before the administration of imipramine. These alert patterns lasted for about 30 minutes. However, the dose of 2 mg/kg of imipramine did not modify the resting pattern in many of the reserpinized animals, and no activation of the alert pattern was found in this dose. The administration of 7 mg/kg produced the resting pattern of the I and II groups in 10 out of 11 animals. These results are demonstrated in Fig. 2 and Table 1. No animal exhibited the dissociation between the cortical and hippocampal EEG by imipramine.

6. Effects of chlorpromazine on the spontaneous EEG in the reserpinized rabbits

The administration of 1 mg/kg of chlorpromazine did not modify the manifestation of the resting pattern in the cortical and hippocampal EEG in most of the reserpinized rabbits. In the rabbits whose EEG showed the alert pattern previously, however, the same dose of chlorpromazine produced the clear-cut resting pattern. The further increase in the dose up to 5 mg/kg did not change the spontaneous EEG or produced a slight modification to the resting pattern in some of the reserpinized animals, as shown in Fig. 3 and Table 2. Chlorpromazine did not cause the dissociation of the EEG between the cortex and hippocampus.

7. Effects on the reticular arousal response

In the intact rabbits, the intravenous injection of imipramine elevated the stimulation threshold of the reticular arousal response, and the mean increase by 2 and 7 mg/kg was about 40% and 100%, respectively, as shown in Figs. 4 and 5. Though the correlation was not found between the previous background activity of the EEG and the threshold change after imipramine, more marked elevation of the threshold was observed in the animals whose EEG showed the marked resting pattern in response to imipramine. Imi-
pramine elevated the threshold of the reticular arousal response less in the reserpinized animals than in the intact ones. The mean increase of the threshold caused by 2 and 7 mg/kg of imipramine in the reserpinized animals was 13% and 56%, respectively.

FIG. 4. Per cent change in the stimulation threshold of the reticular arousal response induced by imipramine and chlorpromazine.

Chlorpromazine also elevated the threshold of the reticular arousal response in the intact rabbits. The mean increase of the threshold caused by 2 and 7 mg/kg of imipramine in the reserpinized animals was 13% and 56%, respectively.

Chlorpromazine also elevated the threshold of the reticular arousal response in the intact rabbits. The mean increase was 36% by 1 mg/kg of chlorpromazine and 54% by 5 mg/kg, as shown in Figs. 4 and 6. The increased dose of chlorpromazine resulted in the progressive elevation of the threshold, though the spontaneous EEG did not progress the manifestation of the resting pattern. The elevation of the threshold caused by chlorpromazine was less in the reserpinized animals than in the intact ones. The mean in-
crease of the threshold of the reticular arousal response by 1 and 5 mg/kg of chlorpromazine in the reserpinized animals was 13% and 27%, respectively.

8. Effects on the recruiting response

In about 2/3 of the intact rabbits, the stimulation threshold of the recruiting response showed a slight increase by the administration of imipramine, and the mean elevation of the threshold by 2 and 7 mg/kg was 4% and 11% respectively, as shown in Figs. 7 and 8. Some correlation was found in the effects of imipramine between the manifestation of the resting pattern in the EEG and the elevation of the threshold. In the reserpinized animals, the mean increase of the threshold of the recruiting response by 2 and

![Diagram showing effects of imipramine and chlorpromazine on EEG patterns in rats.](image)

**Fig. 6.** Effect of chlorpromazine on the reticular arousal response (Mesencephalic reticular formation: 200/sec, 1 msec, 6 sec) of the non-treated and reserpinized rabbits. Calibration: Ordinate 100 µV, abscissa 1 second.

**Fig. 7.** Per cent change in the stimulation threshold of the recruiting response induced by imipramine and chlorpromazine.
7 mg/kg of imipramine was only 3% and 5%, respectively. Though the changes of the threshold in both intact and reserpinized animals were not significant, the reserpinization was likely to depress the elevating effect of imipramine on the threshold.

Chlorpromazine in the dose of 1 mg/kg decreased slightly the threshold of the recruiting response in a few intact rabbits. In most of the animals, however, the threshold was not changed by 1 and 5 mg/kg. The mean changes of the threshold by 1 and 5 mg/kg of chlorpromazine were −1.5% and 2% within the physiological deviation. The mean increase of the threshold was 4% by 1 mg/kg of chlorpromazine and 9% by 5 mg/kg, in the reserpinized animals. There was some correlation in the effects of chlorpromazine between the manifestation of the resting pattern in the EEG and the elevation of the threshold in many of the animals. These results are shown in Figs. 7 and 9.

![Fig. 8. Effect of imipramine on the recruiting response (Nucl. centre médian of thalamus 8/sec, 1 msec, 6 sec) of the non-treated and reserpinized rabbits. Calibration: Ordinate 100 µV, abscissa 1 second.](image)

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![Fig. 9. Effect of chlorpromazine on the recruiting response (Nucl. centre médian of thalamus 8/sec, 1 msec, 6 sec) of the non-treated and reserpinized rabbits. Calibration: Ordinate 100 µV, abscissa 1 second.](image)
In the reserpinized rabbits, the cortical and hippocampal EEG tended to the resting pattern. Kikuchi (8) in this laboratory has reported that the intravenous injection of 0.5 to 1 mg/kg of reserpine produces the resting pattern in the spontaneous EEG within 30 minutes, and then, the EEG turns into the alert pattern in the rabbit, though the animals exhibits the behavioral sedation. The dissociation between the spontaneous EEG and behavior was observed until 18 hours after the administration of reserpine. The alert pattern of the spontaneous EEG by reserpine has also been reported in the acute preparations by Rinaldi et al. (9) and Gangloff et al. (10). Pscheidt et al. (11) have indicated that the spontaneous EEG in the restrained rabbits turns to the alert pattern at 3 to 6 hours after the fixation, and therefore, the alert pattern in the animals treated with 1 to 5 mg/kg of reserpine can not be differentiated from the same pattern in the non-treated ones at least from 3 hours after the fixation. Further, they have shown the different responses on the EEG to reserpine according to the pre- or post-surgical administration. The pre-surgical administration of reserpine produced the resting pattern of the EEG at 5 hours after the injection of reserpine, and this resting pattern did not turn to the alert one even by painful stimulation. Since the reserpinization in the present experiments was the pre-surgical administration, the results coincided well with those in the pre-surgical reserpinized animals described by Pscheidt et al. (11).

The release and depletion of monoamines in the brain by reserpine have been demonstrated by many investigators (12–15). This evidence is indicative for the dual nature of the effect of reserpine on the brain activity and consequently on the EEG. The assumption that the increased level of free monoamines in the brain by reserpine causes the initial alert phase in the reserpinized animals is supported by the observation of Costa et al. (16) that the manifestation of the alert pattern of the EEG in the animals treated with amphetamine and monoamine oxidase inhibitors associates with the increased level of the brain monoamines. On the other hand, the late manifestation of the behavioral sedation and the resting pattern in the spontaneous EEG in the reserpinized animals is presumably due to the depletion of the tissue monoamines. Klerman et al. (17) have supported the preferential contribution of the role of endogenous catecholamines in the central nervous system to the reserpine sedation rather than the role of endogenous serotonin.

The manifestation of the resting pattern in the EEG by 7 mg/kg of imipramine in the present experiments accorded well with the results presented by several investigators (18). However, small dose (0.2 mg/kg) of imipramine produced the alert pattern in half of the intact rabbits. The behavioral wakefulness and the alert pattern of EEG were also observed by Sigg (19) in the cats received 0.3 mg/kg of imipramine. The manifestation of the resting pattern in the EEG by 1 to 5 mg/kg of chlorpromazine irrespective of the previous background activity was in the same line with the results shown by many workers (10, 20). Some dissociation of the EEG effects between the cortex and the
hippocampus was observed in a few animals treated with either agent.

Imipramine produced the EEG changes in the reserpinized rabbits as similar as in the intact one; i.e. the alert pattern in the dose of 0.2 mg/kg and the resting pattern in the doses above 2 mg/kg. The reserpinized animals did not behave differently in the spontaneous EEG from the intact animals to any doses of chlorpromazine. Therefore, it is likely that the depletion of the brain monoamines by reserpine is not a prerequisite for the manifestation of the resting pattern of EEG by imipramine and chlorpromazine.

Imipramine and chlorpromazine elevated the threshold of the reticular arousal response in both intact and reserpinized rabbits. In the reserpinized animals, however, the increase in the threshold by either agent was slightly less than that in the intact animals. These results suggested that the reserpinized animals are less sensitive to the depressing effects of either agent. However, Kikuchi (8), Gangloff et al. (10) and Killam (20) have reported that reserpine also depressed the reticular arousal response. The less elevation of the threshold by imipramine and chlorpromazine in the reserpinized animals may derive at least partly from the reserpine effect itself.

The threshold of the recruiting response in the intact rabbits was apparently elevated by imipramine but not by chlorpromazine. The marked depression of the recruiting response during the alert state caused by stimulation of the reticular formation or during the natural awaking state has been presented by several workers (21–23). Dell et al. (24) and Bradley et al. (25) have shown a hypothesis that the synaptic transmission in the thalamus is cholinergic and that in the midbrain is adrenergic. Recently, Benešová et al. (26–28) have reported that the antidepressants such as imipramine and monoamine oxidase inhibitors decrease the duration of the arousal response to physostigmine, while the tranquilizers such as chlorpromazine and reserpine increase it. They have concluded that the antidepressants exhibit the central anti-cholinergic effect and tranquilizers show the central anti-adrenergic effect. In the present experiments, the relatively preferential effects of imipramine on the recruiting response suggested some direct action on the thalamic mechanism. The depressive effect of imipramine on the recruiting response was less in the reserpinized animals than that in the intact ones, while the inhibitory effect of chlorpromazine on the recruiting response was only observed in the reserpinized animals. The initial facilitation of the recruiting response followed by the depression from 1 to 2 hours after the administration of reserpine was observed by Kikuchi (8) and Gangloff et al. (10). The difference between the imipramine and chlorpromazine effects on the recruiting response of the reserpinized animals indicated the potentiating effect between reserpine and chlorpromazine but not between reserpine and imipramine, and was roughly in accord with the results presented by Stein et al. (29) and Horovitz et al. (30).

The antagonistic effects between reserpine and imipramine or chlorpromazine on the autonomic responses have been presented (31, 32). Imipramine and adequate doses of chlorpromazine blocked the hypothermia, ptosis, bradycardia and diarrhea caused by reserpine in rats, but did not block the depletion of the brain catecholamine by reserpine. It has been reported by several investigators (29, 30, 33–35) that the behavioral
effects of amphetamine are potentiated by imipramine but antagonized by chlorpromazine. Stein et al. (29) have observed the augmenting and prolonging effect of imipramine and the blocking effect of chlorpromazine on the reward response of the hypothalamic self-stimulation of rats to amphetamine. Using the cats with implanted electrodes into the lateral hypothalamus, Horovitz et al. (30) have found the synergism between imipramine and amphetamine on the frequency of the self-stimulation and the antagonism between chlorpromazine and amphetamine. Scheckel et al. (34) have also reported that imipramine potentiates the effect of amphetamine and cocaine on the continuous avoidance response in rats, but chlorpromazine is inactive in this respect. These findings suggest that imipramine produces the stimulant or antidepressive effects by sensitizing the central mechanism of free or active catecholamine in the brain, as also indicated by Sigg (2) in the peripheral structures. On the other hand, chlorpromazine may exert the anti-adrenergic effect in the central nervous system.

Imipramine is also ascribed to inhibit the uptake of catecholamine in the storage granules and to block the inactivation of the free amines at the receptor sites (17). These assumption are supported by the clinical evidence that the combined administration of imipramine and reserpine produce a marked improvement of the depressive symptoms even in the refractory patients to imipramine alone (36).

SUMMARY

The effects of intravenous injection of imipramine and chlorpromazine on the spontaneous EEG, reticular arousal response and recruiting response were comparatively investigated in the intact and reserpinized animals. The dose of 1 mg/kg of reserpine was administered intraperitoneally about 24 hours before the surgical procedures.

1. The spontaneous EEG in the motor cortex and hippocampus turned to the alert pattern by 0.2 mg/kg of imipramine in half of the intact animals and reserpinized ones. The doses above 2 mg/kg of imipramine produced the resting pattern, and the level of the resting pattern was dose-dependent. The appearance of the resting pattern caused by 1 to 5 mg/kg of chlorpromazine was relatively uniform and dose-independent.

2. The previous reserpinization of the rabbits increased the number of animals showing the resting pattern of EEG. Imipramine and chlorpromazine did not produce significantly different effects on the EEG between the intact and reserpinized animals.

3. Imipramine and chlorpromazine elevated the threshold of the reticular arousal response proportionately to the doses in the intact animals. The reserpinization of the animals depressed the elevation of the threshold by either agent.

4. The threshold of the recruiting response was slightly elevated by imipramine in both intact and reserpinized animals, while the similar elevation by chlorpromazine was observed only in the reserpinized animals.
REFERENCES