EFFECT OF PSYCHOTROPIC DRUGS ON CATECHOLAMINES IN BRAIN AND ADRENAL MEDULLA OF RATS UNDER STRESS PRODUCING PEPTIC ULCERS

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It is well known that physical stress such as electroshock, exercise, immobilization, cold exposure, etc., produce significant alterations of catecholamine (CA) metabolism in the brain and adrenal medulla. The findings vary however with different types and intensities of stress used. Some investigators have reported the depletion of brain norepinephrine (NE) by cold exposure or electroshock (1, 2). Others have reported the elevation of brain NE by repeated electroshock, restraint, or cold exposure (3-5). Gordon et al. (6) observed an appreciable decrease in adrenal epinephrine (EP) despite little change in brain NE level by exercise.

On the other hand, Fujiwara and Mori (7) found that tetrabenazine and reserpine worsened stress-induced ulcers and that a MAO inhibitor prevented ulcers. This finding suggests that stress-induced ulcers correlate with an alteration in the central endogenous amines. It has also been found that chlorpromazine (CPZ) and imipramine have preventive effects on stress-induced ulcers (8-10), however effects of these drugs on CA metabolism under particular conditions have been little investigated.

The purpose of the present study was to examine the change of CA levels in the brain and adrenal medulla of rats subjected to stress producing peptic ulcers, and also the effects of psychotropic drugs on CA levels in the state.

METHODS

Male rats of the Wistar strain weighing 230-260 g were subjected to stress inducing peptic ulcers. Each rat was immobilized in a compartment of a stress cage, which was then immersed for 20 hr vertically to the height of the xiphoid of rat in a water bath kept at 23°C (11). Non-stressed rats were kept without food and water in a cage for 20 hr.

CPZ HCl 30 mg/kg, imipramine HCl 30 mg/kg and phenobarbital Na 100 mg/kg was respectively injected intraperitoneally (i.p.) just before rats were subjected to stress.

After the rats were sacrificed by cervical dislocation, the brains and adrenal glands were removed and separately homogenized in glass homogenizers containing 10 ml of 0.04 M perchloric acid solution. Brain NE, dopamine (DA), adrenal NE and EP were determined fluorometrically by the method of Anton and Sayre (12, 13). Recovery of NE and
EP by this method was 75-80% and of DA was 70-75%.

Splanchnic nerve dissection on the left side was performed under 0.1 ml 5% pentobarbital sodium anesthesia (i.p.) 14 days before the stress treatment.

RESULTS

1. Development of peptic ulcers

All rats subjected to stress revealed macroscopically gastric lesions consisting of erosions and extensive hemorrhage. In CPZ- and imipramine-pretreated rats no erosion was observed, only a slight hemorrhage in the gastric wall. Phenobarbital did not affect stress-induced ulcers.

2. Effect of stress on brain NE and DA

The effects of the stress alone and the stress plus psychotropic drugs on the brain NE and DA are shown in Table 1. Rats subjected to stress showed a significant depletion in brain NE (from 0.27 μg/g to 0.24 μg/g), which was accelerated by CPZ-pretreatment (0.21 μg/g) and prevented by imipramine-pretreatment (0.28 μg/g). Phenobarbital did not alter the stress-induced depletion. In contrast to NE, DA in brain neither decreased under stress nor changed under pretreatments with psychotropic drugs. In non-stressed rats, pretreatments of psychotropic drugs did not affect either brain NE or DA levels.

| Pretreatment  | NE (μg/g ± S.E.) | DA (μg/g ± S.E.) |
|--------------|----------------|----------------|
|              | Non-stressed   | Stressed       | Non-stressed | Stressed |
| No-treatment | 0.27 ± 0.005(4) | 0.24 ± 0.004*  | 0.59 ± 0.02 (6) | 0.61 ± 0.02 (7) |
| Chlorpromazine (30 mg/kg) | 0.28 ± 0.019(4) | 0.21 ± 0.004**(6) | 0.54 ± 0.01 (4) | 0.56 ± 0.02 (5) |
| Imipramine (30 mg/kg) | 0.27 ± 0.005(4) | 0.28 ± 0.001**(6) | 0.60 ± 0.04 (6) | 0.54 ± 0.02 (7) |
| Phenobarbital (100 mg/kg) | 0.28 ± 0.01 (5) | 0.25 ± 0.01 (5) | 0.58 ± 0.03 (5) | 0.57 ± 0.03 (7) |

Numbers in parentheses refer to number of animals.
* p<0.001 when compared with non-stressed rats.
** p<0.001 when compared with untreated rats.
All data are uncorrected.

| Pretreatment  | NE (μg/pairs ± S.E.) | EP (μg/pairs ± S.E.) |
|--------------|----------------|----------------|
|              | Non-stressed | Stressed       | Non-stressed | Stressed |
| No-treatment | 2.07 ± 0.22 (6) | 1.48 ± 0.12*(8) | 12.16 ± 0.51 (6) | 5.41 ± 0.67** (8) |
| Chlorpromazine (30 mg/kg) | 2.50 ± 0.43 (5) | 1.96 ± 0.28 (8) | 11.64 ± 0.74 (5) | 4.48 ± 0.67 (8) |
| Imipramine (30 mg/kg) | 2.66 ± 0.51 (5) | 1.93 ± 0.34 (6) | 12.86 ± 0.34 (5) | 8.55 ± 0.23*** (6) |
| Phenobarbital (100 mg/kg) | 1.99 ± 0.18 (5) | 1.38 ± 0.28 (5) | 14.36 ± 1.20 (5) | 7.38 ± 0.99 (5) |

Numbers in parentheses refer to number of animals.
* p<0.05 when compared with non-stressed rats.
** p<0.001 when compared with non-stressed rats.
*** p<0.01 when compared with untreated rats.
All data are uncorrected.
3. Effect of stress on adrenal NE and EP (Table 2)

In non-stressed rats, CPZ, imipramine and phenobarbital did not significantly affect adrenal NE and EP levels. Stressed rats revealed considerable depletion of both adrenal NE (from 2.07 µg/g to 1.48 µg/g) and EP (from 12.16 µg/g to 5.41 µg/g). Depletion of adrenal EP was prevented by imipramine-pretreatment, but CPZ- or phenobarbital-pretreatments showed insignificant effects.

4. Effect of left splanchnic denervation on depletion of adrenal CA by stress

In order to determine whether the CA liberation from the adrenal medulla by stress is brought about by a neural or hormonal factor, dissection of the splanchnic nerve innervating the adrenal gland was carried out on some rats prior to stress situation. As shown in Fig. 1, there was no significant difference in CA levels between the innervated right and denervated left adrenal glands in non-stressed rats, however in stressed rats, there was a significant difference in both NE and EP levels between the right and left adrenal glands. Depletion of CA contents by stress was almost completely inhibited in the denervated left adrenal gland.

![Diagram showing NE and EP levels in non-stress and stress conditions, denervated and innervated glands.](image)

**Fig. 1.** Effect of denervation of left splanchnic nerve on adrenal catecholamine levels in rats.

Denervation was performed 14 days before stress treatment. Each column and vertical bar represent mean value and standard error respectively. *P<0.01 when compared with right adrenal gland of stressed rats. **P<0.001 when compared with right adrenal gland of stressed rats.

**DISCUSSION**

As shown in Table 1, the stress producing peptic ulcers induced a decrease in brain NE, but no change in brain DA. This is in agreement with findings reported by Bliss et al.
(2) that electroshock to the feet induced a great decrease in the level of brain NE but did not alter the concentration of brain DA.

One of the aims in this study was to ascertain the hypothesis that decrease of central amines could correlate in production of stress-induced ulcers (7). The following results in this experiment appeared to support the hypothesis; 1) rats subjected to the stress showed decrease of brain NE, 2) imipramine prevented decrease of NE as well as preventing peptic ulcers, 3) in contrast to imipramine, phenobarbital had no effect on either. CPZ, however accelerated depletion of brain NE, although it had the preventive effect on peptic ulcers. This suggests that stress-induced ulcers do not correlate only with central CA levels. There was also no interrelation between stress-induced ulcers and the changes of adrenal CA levels. To define the relation between production of stress-induced ulcers and CA, further investigations such as examining CA turnover are necessary.

CPZ, imipramine and phenobarbital each of which represented neuroleptics, thymoleptics and narcoleptics showed respectively different effects on the stress-induced decrease of brain NE. The different effects may relate to the effects of these drugs on the disappearance rate of brain NE (14, 15). As to the effects of CPZ and phenobarbital on the decrease of brain NE, the data in this experiment are inconsistent with that reported by Maynert and Levi (1) that CPZ and phenobarbital inhibit the electroshock-incited decline in brain NE. This discrepancy could be due to the difference in the kind and duration of stress.

Fig. 1 shows that liberation of CA from the adrenal medulla by stress is regulated substantially by splanchnic nerve activity. This fact suggests that stress primarily stimulates the autonomic nerve center of the hypothalamus, followed by an enhancement of splanchnic nerve activity and liberation of CA from the adrenal medulla. The preventive effect of imipramine on the stress-induced CA liberation from the adrenal medulla (Table 2) is presumably due to depression of central sympathetic activity by the drug followed by a decrease in peripheral sympathetic activity. This is supported by the report that antidepressant drugs reduced or even abolished splanchnic discharges induced by central stimulation in cats (16).

SUMMARY

Stress producing peptic ulcers induced the depletion of brain NE and adrenal CA. Although both CPZ- and imipramine-pretreatment prevented stress-induced peptic ulcers, the former accelerated the depletion of brain NE, the latter conversely prevented it. Phenobarbital neither prevented peptic ulcers nor affected the depletion of brain NE. Brain DA neither decreased by stress nor changed by pretreatments with psychotropic drugs used in this study.

Imipramine prevented the stress-induced depletion of adrenal EP, although CPZ and phenobarbital had no significant effect. Depletion of adrenal CA by stress was almost completely inhibited by splanchnic nerve dissection.

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