The Effect of Perphenazine on the ACTH Release Induced by Neurotropic Stress*

By

E. Kivalo and U. K. Rinne

(Received November 16, 1959)

Tranquilizing drugs such as chlorpromazine, reserpine and related compounds are of value in the treatment of various types of emotional disturbances in man. In experimental animals, too, they have been found to prevent in a great measure the effects induced by stress, e.g. by inhibiting the strong ACTH release [e.g., Hamburger (1955), Olling and Dewied (1956), Sevy et al. (1957), Mahfouz and Ezz (1958), Mäkelä et al. (1959)].

Recently a new derivative belonging to the chlorphenothiazine group, perphenazine, has been developed, of which group also chlorpromazine is a member. The purpose of the present work was to determine the effect of perphenazine on the ACTH release induced by neurotropic stress. The adrenal ascorbic acid depletion was used as an indicator of ACTH release [Sayers (1950)].

Material and methods

Altogether 147 white male rats weighing about 200 g each were used for experimental animals. They were divided into the following groups of seven animals each:

Acute experiments. 1a. Intact controls. These rats were killed immediately after being taken from the cage and had received no treatment.

1b. Controls to which a subcutaneous injection of 0.2 ml physiological sodium chloride solution was administered 11/2 hours prior to killing.

2. The animals in this group were injected subcutaneously with perphenazine [1-(2-hydroxyethyl)-4-(3-(2-chloro-10-phenothiazyl)-propyl)piperazine,] "Trilafon" in a dosage of 0.5 mg per 100 g body 11/2 hours before killing.

3a. The rats of the neurotropic stress group were kept for one hour each in its own small cage, where they were irritated by means of strong sound and light stimuli.

3b. The animals of the perphenazine + neurotropic stress group were subjected simultaneously, during one hour, to the stimuli described

* Aided by a grant from the Sigrid Jusélius Stiftelse.
above but they were injected, 1/2 hours prior to this, with perphenazine in a dosage of 0.05 mg per 100 g body weight.

4 a. The animals were treated as in Group 3a.
4 b. The animals were treated as in Group 3b except that the perphenazine dosage was 0.1 mg per 100 g body weight.

5 a. The animals were treated as in Group 3a.
5 b. The animals were treated as in Group 3b except that the perphenazine dosage was 0.25 mg per 100 g body weight.

6 a. The animals were treated as in Group 3a.
6 b. The animals were treated as in Group 3b except that the perphenazine dosage was 0.5 mg per 100 g body weight.

7 a. The animals in this group were injected subcutaneously with 5 I.U. ACTH per 100 g body weight and killed after 1 1/2 hours.
7 b. The animals were injected with ACTH like those in the preceding group; additionally they were injected with perphenazine half an hour prior to this, in dosage of 0.5 mg per 100 g body weight.

8 a. The animals were injected subcutaneously with pitressin in a dosage of 1 I.U. per 100 g body weight and killed after 1 1/2 hours.
8 b. The animals in this group were injected with pitressin like those in the preceding group; additionally they were injected with perphenazine half an hour prior to this, in a dosage of 0.5 mg per 100 g body weight.

Chronic experiments. The test animals were injected subcutaneously with 0.5 mg perphenazine per 100 g body weight daily. On the third, fifth and 9th day of treatment, half an hour after the perphenazine administration, seven animals in each instance were subjected to neurotropic stress during one hour in the same manner as the rats of the acute test groups (Groups 3 to 6) and killed thereafter. On each one of the above-mentioned days a corresponding number of rats were also simultaneously subjected to the same kind of neurotropic stress during one hour without any preceding treatment and subsequently killed.

All the animals were killed by rapid decapitation. The adrenals were immediately removed from the surrounding tissue and weighed on the torsion balance. They were then homogenized in 4% trichloracetic acid and their ascorbic acid content was determined according to Schaffert and Kingsley (1955).

Statistical treatment. The t-test was employed in the statistical treatment of the results. The difference between the means was considered to be statistically significant when the value of $P$ was $\leq 0.05$.

Results

It can be seen from Table 1 that injection of mere physiological sodium chloride solution induced adrenal ascorbic acid depletion, but