EFFECT OF LYSYL-VASOPRESSIN AND VASOTOCIN ON DISTURBANCE OF AVOIDANCE CONDITIONING BY SEROTONIN RECEPTOR BLOCKER CYPROHEPTADINE

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KEY WORDS: vasopressin; vasotocin; cyproheptadine; avoidance reflex.

The role of pituitary posterior lobe hormones and their analogs in the mechanisms of memory is currently the subject of much careful investigation [5, 7-9]. It has been shown that lysyl- and arginyl-vasopressins delay extinction of a conditioned avoidance reflex (CAR), potentiate the passive avoidance reflex, and abolish retrograde amnesia. Meanwhile the effect of these hormones on the rate of CAR formation has received less study, and it is usually stated that this effect is small. However, considering that the neuropeptides possess regulatory properties, it may be expected that pituitary hormones will be more active against the background of drug-induced disturbances of normal processes.

Considering the role of serotoninergic processes in the mechanisms of CAR [2], avoidance conditioning was studied after blocking of serotonin receptors by cyproheptadine, and the effect of lysyl-vasopressin and vasotocin on this process was examined. The latter compound has comparatively weak action on CAR extinction [9], but has a considerable effect on animal behavior [3].

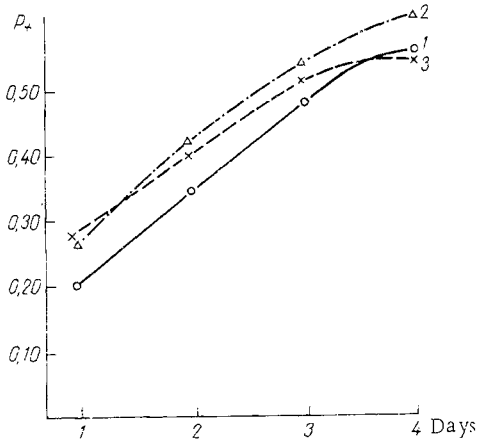

Fig. 1. Time course of CAR formation in control animals (1) and during daily administration of LVP (2) and AVT (3) in a dose of 10^{-3} mg/kg. Abscissa, time of training (in days); ordinate, values of P_+.

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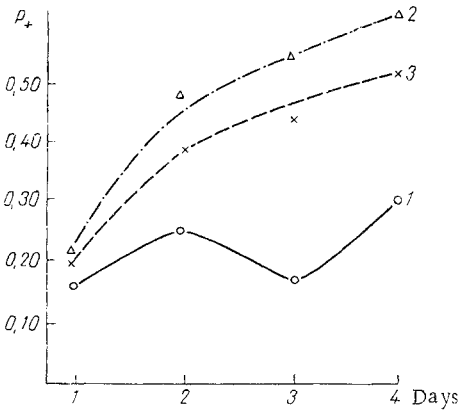

Fig. 2. Changes in number of avoidances during CAR formation accompanied by daily injection of cyproheptadine alone (1) and cyproheptadine together with LVP (2) and AVT (3). Legend as to Fig. 1.

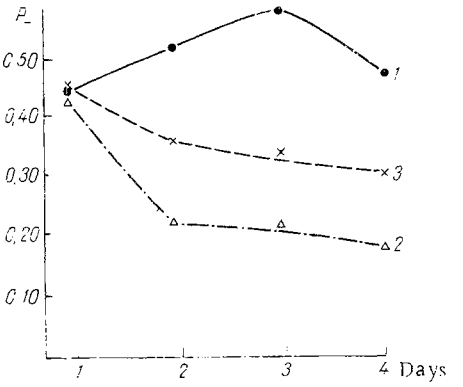

Fig. 3. Changes in number of absences of escape during CAR formation accompanied by daily administration of cyproheptadine alone (1) and cyproheptadine together with LVP (2) and AVT (3). Abscissa, time of training (in days) ; ordinate, values of P_-.

EXPERIMENTAL METHOD

Noninbred male albino rats weighing 150-250 g were used. Lysyl^8-vasopressin (LVP) and arginyl^8-vasotocin (AVT) in a dose of 10^{-3} mg/kg and cyproheptadine in a dose of 1 mg/kg were injected intraperitoneally in aqueous solution ; control animals received distilled water. All these preparations were from Serva, West Germany.

The CAR formed in the animals consisted of jumping on a shelf after presentation of a conditioned acoustic stimulus. Electric shocks were applied to the skin through the electrified floor for 30 sec, 5 sec after acoustic stimulation. The number of avoidances (jumping on to the shelf before switching on the power) and the number of escapes (jumping during application of shocks) were counted. Training took place for 4 days, with 10 combinations daily.

To assess the efficacy of training two parameters were used : the relative number of avoidances ($P_+ = n_+/10N$) and the relative number of absences of escape($P_- = n_-/10N$), where n_+ is the total number of avoidances by all animals of the group, n_- the total number of absences of escape, and N the total number of animals in the group.

The coefficient 10 is introduced because the daily session consisted of 10 combinations. Absence of escape was taken to mean when, during 30 sec of application of electric shocks, the animal failed to jump on to the shelf.

LVP and AVT were injected immediately after the end of the training session and cyproheptadine 5 min before the session began.

The statistical significance of the results was estimated by the chi-square test [1].

EXPERIMENTAL RESULTS

Neither LVP nor AVT had any significant effect on the speed of CAR formation (Fig. 1). The time course of learning in the group of animals receiving LVP (21 rats) and in the group receiving AVT (15 rats) was virtually indistinguishable from that of the control animals (30 rats). There was no difference between these groups either with respect to the parameter P_-.

Administration of cyproheptadine sharply impaired the ability of the animals to learn, as reflected in both parameters. The number of avoidances in this group (24 animals) did not increase until the 4th day of training (Fig. 2), whereas according to the P_- level, there was no progress whatever throughout the 4 days (Fig. 3).

LVP (20 animals) completely restored CAR formation, when disturbed by cyproheptadine, to normal ($P < 0.001$) as regards both the number of avoidances and the number of escapes (Fig. 3). The difference was well marked starting on the 2nd day of learning.

AVT (13 animals) also had a positive effect on the time course of training, when disturbed by cyproheptadine, although its effect was significantly ($P < 0.05$) weaker than that of LVP. Nevertheless, differences in the learning ability of animals receiving AVT together with cyproheptadine and of animals receiving cyproheptadine alone were significant on every day of training (for the 2nd day $P < 0.05$, for the 3rd day $P < 0.001$, for the 4th day $P < 0.01$). The results are evidence of the positive effect of both compounds studied on CAR formation when disturbed by serotonin receptor blockade. This effect must be considered as intervention in the mechanisms of memory, for the action of the hormones on behavior of the animals in the experimental chamber can be ruled out because they were given after the training session.

In the present experiments, just as in those reported in the literature [9], LVP was more active than AVT, for the latter only partially restored the disturbed process of CAR formation.

The disturbing effect of cyproheptadine on CAR formation must also be taken to be connected with memory processes, for the present experiments showed that it had no action, in the dose used, on the animals' motor activity, and also that it has an inhibitory effect on CAR formation when administered after the training session, although this effect was weaker than when the drug was given before the training session.

The question of whether the action of these hormones is connected with their intervention directly in serotoninergic processes remains uncertain. The role of catecholaminergic mechanisms in the action of these substances has recently been demonstrated [4, 6]. The authors cited above consider that the effect observed after injection of the substances into the dorsal raphe nucleus is mediated by catecholamines [4]. In that case, the deficiency of CAR formation due to blockade of serotonin receptors must be considered to be compensated by the catecholaminergic system. However, it must be noted that because of the lack of convincing data on the effect of pituitary hormones on mediator processes and the role of various mediators in memory mechanisms, this problem requires further investigation.

Already considerable clinical evidence of the antiamnesic effects of vasopressin has now been obtained. The abolition of the inhibitory action of cyproheptadine on ability to learn, by vasopressin analogs, described in this paper is yet another argument in support of a study of clincial trials of vasopressin in various memory disturbances associated with CNS dysfunctions.

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EFFECT OF HIGH-ALTITUDE HYPOXIA ON EFFECTIVENESS OF TUMOR CHEMOTHERAPY

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It was shown previously that high-altitude hypoxia inhibits tumor growth [3, 6]. In the investigation described below the response of tumors to chemotherapy in a high mountain environment was studied in order to investigate the antitumor effect of combined action of a chemotherapeutic agent and high-altitude hypoxia. We were motivated mainly by the fact that cytostatic compounds depress the functions of the blood system and lower nonspecific resistance, whereas high-altitude hypoxia stimulates hematopoiesis and increases the reserve powers of the body [1, 8, 9].

EXPERIMENTAL METHOD

Experiments were carried out on 165 noninbred albino rats of both sexes weighing initially 100-120 g. A Guérin carcinoma (series I) or sarcoma 45 (series II) was inoculated subcutaneously into the right side of the animals in the city of Frunze (760 m above sea level). Eight days after inoculation half of the animals were taken up to the Tuya-Ashu Pass (3200 m above sea level). Both in the plains and in the mountains some animals were treated by chemotherapy and the rest were untreated. Rats with a Guérin carcinoma were treated by intramuscular injections of thio-tepa in a dose of 2 mg/kg every other day, starting on the 10th day after inoculation (seven injections). Rats with sarcoma 45, starting on the 12th day after inoculation, received daily intramuscular injections of 7 mg/kg cyclophosphamide for 2 weeks. The hemoglobin concentration, erythrocyte, leukocyte, and platelet counts, and the leukocyte formula were calculated by the usual methods. The carcinolytic activity of the blood serum [5] and the blood concentration of sulfhydryl (SH) groups [7] also were studied. In each series of experiments the rats were killed at the same times on Tuya-Ashu Pass and in Frunze: animals with Guérin carcinoma on the 23rd day, rats with sarcoma 45 on the 26th day after inoculation. At autopsy the body weight and the weight of the thymus and the tumor were determined. The percentage inhibition of tumor growth and index of effectiveness of chemotherapy [4] were calculated from the weight of the tumor.

EXPERIMENTAL RESULTS

Growth of the Guérin carcinoma in the control rats was inhibited by 53.3% by exposure for 14 days to high-altitude hypoxia. The weight of the tumor in the animals in Frunze was 22.74 ± 4.3 g, compared with 10.6 ± 2.78 g on Tuya-Ashu Pass ($P < 0.05$). In the high-mountain environment, treatment of Guérin carcinoma with thio-tepa was more effective. For instance, whereas in Frunze the weight of the tumor was reduced by 12.3 times under the influence of thio-tepa (1.85 ± 0.42 g), on Tuya-Ashu Pass it was reduced by 28.1 times (0.81 ±

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