EFFECT OF THE ANXIOLYTICS BUSPIRONE AND DIAZEPAM ON BLOOD PROLACTIN, TSH, AND CORTISOL LEVELS IN GREEN MONKEYS

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Buspirone, a compound of the azospirodecanedione series, is a promising anxiolytic drug, equal in power to diazepam with respect to several pharmacological parameters, but without any hypnotic and muscle-relaxing activity [8]. The biochemical mechanisms of action of buspirone and of anxiolytics of the benzodiazepine series have been shown to differ in principle. In particular this agent evidently does not affect the GABA-benzodiazepine receptor complex [10]. A study of the neuroendocrine effect of buspirone has shown that it is a powerful stimulator of prolactin secretion into the bloodstream in man and rats [7].

Since we know [4] that diazepam does not increase the prolactin release into the blood, it is important to undertake a direct comparison of the effects of buspirone and diazepam on this parameter.

The aim of the present investigation was to obtain relevant data, and also to study the effect of buspirone on several other hormones (TSH, cortisol).

EXPERIMENTAL METHOD

Experiments were carried out on male green monkeys (*Cercopithecus aethiops*) weighing 2.5-3.5 kg. Each animal was kept in a separate cage, but the cages were placed in the same room. The animals received food three times a day.

Buspirone and compound MJ 138-05, obtained from Bristol-Myers Company (USA) in the form of pure substances, were dissolved before the experiments in sterile physiological saline. Diazepam was used in the form of the solution for injection (Seduxen, Hungary), which was mixed before the experiment with physiological saline to obtain the necessary concentration. The drugs were injected intramuscularly in a volume of 1 ml between noon and 1 p.m. Control animals were given an injection of physiological saline. At the time of the injection the animals were fixed for 1-2 min to the front wall of the cage. The animals were again immobilized 30-40 min after the injection and 2-3 ml of blood was taken from the femoral vein into the polystyrene test tubes containing heparin. Plasma was obtained by rapid centrifugation at 1000g for 10 min and kept at −20°C for not more than 2 weeks. Before the investigation the plasma was thawed, centrifuged for 10 min at 10,000g, and the supernatant was used for the work. Concentrations of prolactin, TSH, and cortisol were determined by radioimmunoassay using kits from Pharmos (Finland). For cortisol assay one-third of the volume of plasma recommended by the manufacturer was used, because the blood cortisol level in green monkeys is much higher than in man.

EXPERIMENTAL RESULTS

The animals were not anesthetized for the experiments and were not put to sleep. Consequently, the hormone levels determined in plasma of the control animals did not correspond to their basal level in that particular animal, but reflected the hormone concentrations during exposure to an average degree of stress, due to blood sampling and injection of the drugs. The action of the anxiolytics correspondingly was studied against the background of stress. In all doses used (2.5-10 mg/kg) buspirone caused the plasma prolactin level of the animals

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TABLE 1. Plasma Prolactin, TSH, and Cortisol Levels in Green Monkeys after Administration of Drugs (M ± m, n = 4-6)

Experimental conditions	Dose of drug, mg/ml	Prolactin, mIU/liter	TSH, mIU/mIU/liter	Cortisol, nmoles/liter
Control	—	398±85	1,53±0,43	1554±81
Buspirone	3	2785±324*	—	—
	5	3065±544*	1,74±0,21	1446±176
	10	3075±466*	1,75±0,56	1497±72
MJ 138-05	5	420±232	2,83±1,4	1779±553
	10	1274±375**	1,78±0,28	2132±221
Diazepam	1	175±61	1,15±0,17	1114±147

Legend. In each experiment 4-6 animals were used. *P < 0.01, **P < 0.05.

to rise considerably (tenfold) 30 min after injection (Table 1, Fig. 1). The buspirone analog MJ 138-05, in a dose of 10 mg/kg, raised the plasma prolactin level in three of the animals tested (Fig.1a), whereas in a dose of 5 mg/kg it had no significant effect (Table 1). Diazepam (1 mg/kg) lowered the prolactin concentration, but not statistically significantly. The much greater scatter of the data in the group of animals receiving buspirone will be noted compared with the control and with animals receiving diazepam.

The study of TSH levels revealed no difference between the control and the experimental groups (Fig. 1b; Table 1).

The cortisol level fell by 35% (Table 1a) after administration of diazepam (1 mg/kg) but was unchanged after buspirone (5 and 10 mg/kg). Injection of MJ 138-05 in a dose of 10 mg/kg caused a 40% increase in the cortisol concentration (not statistically significant). The cortisol level in animals receiving MJ 138-05 in a dose of 5 mg/kg was the same as in the control.

Observations on the animals' behavior showed that buspirone (3 and 5 mg/kg) and diazepam (1 mg/kg) had a marked antiaggressive effect. The animals ceased to demonstrate aggressive and challenging postures, were more approachable by human beings, and their excitability and spontaneous and reflex aggressiveness were reduced. Buspirone, in a dose of 10 mg/kg, had a similar but stronger action. MJ 138-05 had not only an antiaggressive effect, but (in a dose of 10 mg/kg) also gave rise to various behavioral responses — from muscle relaxation to tremor and motor excitation, with elements of pseudohallucinatory behavior.

The results thus showed that buspirone stimulates prolactin release into the bloodstream of green monkeys, in agreement with results obtained previously on rats and man [6, 7]. It has been suggested [5-7] that the most probable mechanism of action of buspirone is to block dopaminergic pathways inhibiting prolactin secretion. This hypothesis is confirmed by the ability of buspirone to inhibit binding of spiroperidol and N-propylapomorphine with dopamine D-2 receptors (IC_{50} = 200-400 nM) [8]. Incidentally, compound MJ 138-05, which has an anxiolytic action similar to that of buspirone, has no affinity for dopamine receptors [11]. The probable effect of buspirone on the serotoninergic system, activation of which also stimulates prolactin release [3], cannot be ruled out. This hypothesis is in agreement with data on the ability of buspirone to interact with serotonin receptors [1, 3, 8].

Convincing proof has been obtained that the effect of diazepam on prolactin release is realized through the GABA-benzodiazepine receptor complex [4]. However, the level at which this action takes place has not been identified: directly in the tissue of the pituitary gland or through the involvement of other structures. For example, it may be that diazepam inhibits serotoninergic neurons that stimulate prolactin release. This hypothesis is supported by abundant data on the effect of benzodiazepines on serotonin metabolism in the brain [5].

Buspirone does not affect the plasma cortisol level in green monkeys, but MK 138-05 in a dose of 10 mg/kg actually raises it a little. Meanwhile diazepam lowers the cortisol level, in good agreement with data in the literature [4, 9]. These results point to differences in the character of action of buspirone and diazepam on the secretion of ACTH — the hormone regulating cortisol release.

The results of the present investigation are evidence of qualitative differences in the character of the effect of buspirone and diazepam on secretion of anterior pituitary hormones such as prolactin and, evidently, ACTH.

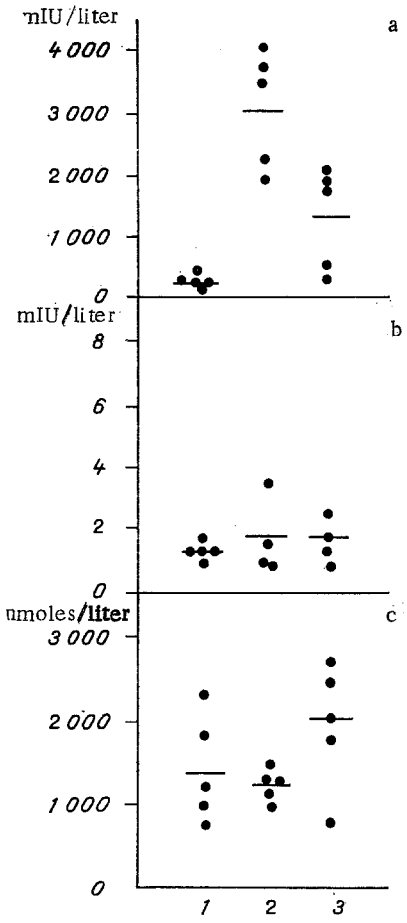

Fig. 1. Plasma prolactin (a), TSH (b), and cortisol (c) levels in green monkeys after administration of buspirone and MJ 138-05. 1) Control (physiological saline); 2) buspirone (10 mg/kg); 3) MJ 138-05 (10 mg/kg).

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LITERATURE CITED

1. A. Ya. Korneev and Chan Thi Binh An, Byull. Éksp. Biol. Med. (1986), (in press).
2. J. A. Clemens, M. E. Ronsh, and R. W. Fuller, Life Sci., 22, 2209 (1978).
3. T. Glaser and J. Traber, Eur. J. Pharmacol., 88, 137 (1983).
4. L. Gradison, Neuropharmacology, 22, 12B, 1505 (1983).
5. W. Haefely, P. P. Pierel, P. Polc, et al., Handbook of Experimental Pharmacology, Vol. 55/11, Berlin (1982), p. 145.
6. H. Y. Meltzer, M. Simonvik, and V. S. Fang, Psychopharmacology, 1, 49 (1982).
7. H. Y. Meltzer, R. Flemming, and A. Robertson, Arch. Gen. Psychiat., 40, 1099 (1983).
8. L. A. Riblet, D. P. Taylor, M. S. Eison, et al., J. Clin. Psychiat., 43, No. 12, 11 (1982).
9. G. Schettini, M. J. Cronin, S. B. O'Dell, et al., Brain Res., 291, 343 (1984).
10. D. P. Taylor, L. E. Allen, J. A. Becker, et al., Drug Dev. Res., 4, 95 (1984).
11. D. Temple, T. Yevich, and J. S. New, J. Clin. Psychiat., 43, 4 (1982).