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Serum corticosterone elevation by pergolide in rats: prevention of tolerance development by spiperone

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Pergolide mesylate, a dopamine agonist (Fuller et al 1979), causes an acute elevation of serum corticosterone concentration in rats (Fuller & Snoddy 1981a). After repeated administration of pergolide, the acute elevation of serum corticosterone is absent or greatly attenuated (Fuller & Snoddy 1981b). Since pergolide-pretreated rats responded to quipazine (an agonist at 5-hydroxytryptamine receptors) with a normal elevation of serum corticosterone, the diminished response to pergolide was suggested to represent subsensitivity of dopaminergic receptors mediating the corticosterone response. To further evaluate that possibility, we determined whether spiperone would prevent this development of tolerance to pergolide.

Methods

Male Wistar rats from Harlan Industries, Cumberland, Indiana, were housed in groups of 5 in a 24 °C room with lights on from 0700–1900 h daily and with food and water freely available for at least 1 week before an experiment. Pergolide mesylate (Eli Lilly and Company, Indianapolis, IN) was injected i.p. at doses of 0·03–0·3 mg kg^{-1}, and spiperone (Janssen Pharmaceutica, Beerse, Belgium) was injected at a dose of 0·1 mg kg^{-1} i.p. Drugs were injected daily at 8 a.m. On day 5, rats were decapitated 1 h after the injection, and serum from trunk blood that had clotted was obtained by centrifugation and stored at −15 °C before analysis. Corticosterone was measured spectrofluorometrically by the method of Solem & Brinck-Johnsen (1965).

Results

The effect of repeated daily treatment with spiperone on the acute elevation of serum corticosterone by pergolide is shown in Fig. 1. Pergolide injection produced a dose-dependent increase in serum corticosterone concentration in rats that had received previous

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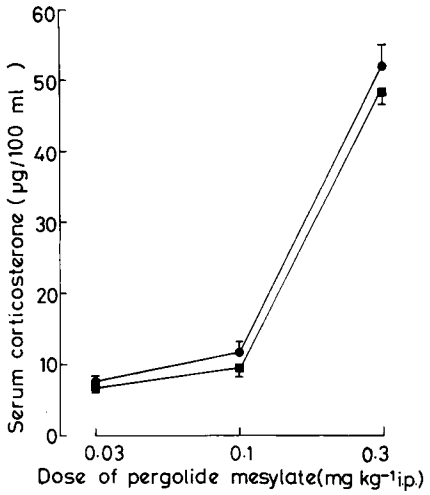

FIG. 1. Dose-dependent elevation of serum corticosterone by pergolide in control (●) and spiperone-pretreated (■) rats. Spiperone (0·1 mg kg^{-1} i.p.) was injected daily at 8 a.m. for 4 days, the last injection being 24 h before the injection of pergolide mesylate. Rats were killed 1 h after pergolide injection. Mean values ± standard errors for 5 rats per group are shown. Control rats receiving vehicle acutely had corticosterone levels of 7·1 ± 0·3 μg/100 ml, and spiperone-pretreated rats receiving vehicle acutely had corticosterone levels of 6·8 ± 0·6 μg ml^{-1}. Statistically significant ($P < 0·05$) increases in corticosterone were produced by the 0·1 and 0·3 mg kg^{-1} dose of pergolide in spiperone-pretreated rats.

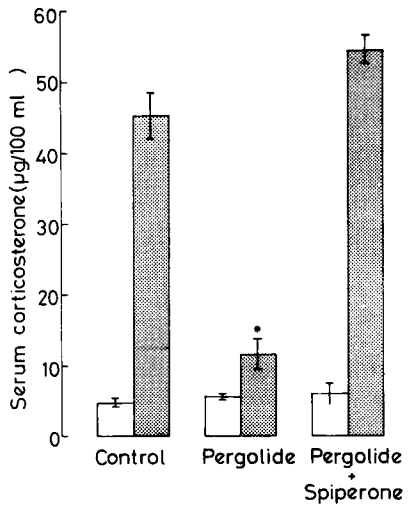

FIG. 2. Elevation of serum corticosterone by pergolide as influenced by prior treatment with pergolide alone or in combination with spiperone. Serum corticosterone was measured 1 h after the acute treatment with pergolide mesylate (0·3 mg kg^{-1} i.p.). Some rats had been pretreated with pergolide alone or with the combination of pergolide and spiperone (0·1 mg kg^{-1} i.p.) daily at 8 a.m. for 4 days, the last pretreatment being 24 h before the terminal treatment (vehicle or pergolide). Mean values ± standard errors for 5 rats per group are shown. Asterisk indicates significant difference from the control group receiving the same acute treatment.

daily injections with spiperone exactly as in control rats. Since this pretreatment with spiperone did not alter the acute response to pergolide, it became possible to do an experiment to see if spiperone given along with daily injections of pergolide would prevent the diminished response to acute pergolide injection. Fig. 2 shows the results of such a study. In control rats, the acute injection of pergolide caused a nine-fold increase in serum corticosterone. In rats pretreated with four daily injections of pergolide, the acute response to pergolide was greatly diminished. A statistically significant increase in corticosterone was produced by pergolide acutely in these rats, but the increase was only two-fold. In rats that had received spiperone along with daily injections of pergolide for four days, the acute injection of pergolide on day 5 again caused a nine-fold increase in serum corticosterone concentration. The decreased responsiveness that had occurred after daily administration of pergolide was totally prevented by daily co-administration of spiperone.

Discussion

These results strengthen the idea that the tolerance to the acute elevation of serum corticosterone by pergolide occurring after repeated treatment with pergolide is in fact related to adaptive changes in dopamine receptors. Previously, we had found that rats given daily injections of pergolide responded to quipazine with a normal rise in serum corticosterone concentration, indicating that corticosterone elevation by an agent acting other than through dopaminergic mechanisms occurred normally (Fuller & Snoddy 1981b). We had also shown that certain other effects of pergolide, e.g. decrease in dopamine turnover and decrease in serum prolactin concentration, showed a normal acute response to pergolide in rats pretreated with daily injections of pergolide (Fuller & Snoddy 1981b). The current finding that a dopamine antagonist, spiperone, prevents the altered responsiveness of the pituitary-adrenocortical system to acute administration of pergolide can most easily be explained by postulating that the diminished responsiveness occurred as a result of continued activation of dopamine receptors. The dopamine receptors that mediate corticosterone elevation by pergolide are believed to be central, since domperidone, which blocks dopamine receptors in the periphery (Laduron & Leysen 1979), is incapable of antagonizing the effect of pergolide (Fuller & Snoddy 1981a). Spiperone blocks the pergolide-induced elevation of corticosterone acutely (Fuller & Snoddy 1981a) and the development of tolerance after repeated pergolide injection, but does not itself cause supersensitivity to the pergolide effect, at least in the experimental conditions used.

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Adsorption of some antibiotics and other drugs on silicone-coated glass surfaces

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Drug adsorption on silicone-coated surfaces and non-coated glass surfaces was studied using porous glass as a reference standard for glass containers. Since glass surfaces coated with silicone can repulse a water layer, it is supposed that silicone-coated surfaces of pharmaceutical glass containers decrease adsorption of drugs. However, in practice, silicone-coated surfaces adsorb more secretin (Ogino et al 1979), insulin, atropine, physostigmine (Mizutani 1981a) and diazepam (Mizutani et al 1981) than non-coated glass surfaces (Mizutani & Mizutani 1978). A loss of potency of diazepam due to its adsorption on plastic i.v. bags has been reported (Parker & MacCara 1980). The purpose of this investigation was to confirm with some widely used antibiotics whether adsorption on silicone-coated glass surfaces as a general phenomenon was greater than that on non-coated glass surfaces. The amounts of drugs adsorbed on silicone-coated glass surfaces and non-coated porous glass surface (CPG-10 240Å, Electro-Nucleonics, Fairfield, N.J., U.S.A.) were estimated by elution of drug solution on columns according to Mizutani & Mizutani (1978). The column size of the non-coated pore glass column was 0·8 cm internal diameter × 4·5 cm length (2·25 ml, 1·12 g of pore glass, surface area 109 m^2) and that of silicone-coated pore glass, which was prepared by the previous method (Mizutani 1980), was 0·68 cm × 3·5 cm (1·26 ml, 0·63 g, surface area 25 m^2).

Drugs were dissolved in pH 7·2 phosphate-buffered saline. Streptomycin sulphate was used at 1 mg ml^{-1} and measured by absorbance at 215 nm. Potassium benzylpenicillin was used at 100 U ml^{-1} and measured