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Adrenal catecholamine concentration after chronic treatment with bromocriptine and haloperidol

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Adrenal catecholamine concentration was measured by HPLC with electrochemical detection in male rats after ten days of bromocriptine and haloperidol (0·05, 0·5 and 5·0 mg kg^{-1}) and vehicle (1·0 ml kg^{-1}) treatments subcutaneously. There were four rats in each group. The results indicate that bromocriptine treatment significantly increased dopamine (DA), noradrenaline (NA) and adrenaline (A) content in a dose-dependent manner. The NA/DA ratio was unchanged, but the A/NA ratio was significantly increased after treatments with two higher doses of the drug. Haloperidol treatment, on the other hand, had no significant effect on dopamine and a biphasic effect on adrenaline content. Noradrenaline concentration increased only after the lowest dose of the drug. There was no significant change in NA/DA or A/NA ratios in any group. The dopamine metabolite, dihydroxyphenylacetic acid (DOPAC), was not detected in any adrenal gland.

Many studies have been reported on the effect of dopamine (DA) agonist and antagonist treatment on brain catecholamines, particularly its metabolism (Kuczenski 1980; Karoum et al 1980; Fuller & Perry 1982). Other studies included both short term (Dichiara et al 1978; Gianutos et al 1976) and long term (Bacopoulos et al 1982; Tsutsumi et al 1982) effects of either agonist or antagonist treatment on brain dopamine metabolism. To our knowledge no study has been reported on the effect of dopamine agonist or antagonist treatment on adrenal catecholamines, particularly the dopamine concentration, except a brief citation by Lackovic & Relja (1984). It is assumed that the concentration of dopamine in the adrenal gland reflects the turnover of noradrenaline (NA) and adrenaline (A) (Waldeck et al 1975) and since they are involved in cardiovascular and other physiological functions and dopamine agonist and antagonist drugs are increasingly being used in the treatment of neurological diseases, we thought it appropriate to study the effect of treatments with a dopamine agonist (bromocriptine) and an antagonist (haloperidol) on adrenal catecholamine concentrations to see if changes in dopamine also influenced noradrenaline and adrenaline concentrations.

Methods

Male Sprague-Dawley rats, 150–200 g, were housed four per cage with free access to food (Ralston Purina Rat Pellets, St Louis, MO, USA) and tap water. The room temperature was 25 °C and the light/dark cycle was controlled with 14 h of light (on at 0300h). The animals were acclimatized for one week before the start of the experiment. Haloperidol (McN-JR-1625, Lot 7701128) and bromocriptine (CB-154, Lot 76002) were gifts from McNeil Laboratories, Inc. (Fort Washington, PA) and Sandoz Pharmaceuticals (East Hanover, NJ), respectively. The drugs were dissolved in dilute glacial acetic acid (pH 3·5) and diluted with distilled water to the required volume and were then injected subcutaneously daily for ten days at three different doses (0·05, 0·5 and 5·0 mg kg^{-1}). The two control groups, one for each drug, received the same volume of the vehicle (1·0 ml kg^{-1}). There were four rats in each group. Twenty-four hours after the last drug and vehicle injection, each rat was decapitated, the abdomen was opened and the adrenal glands immediately removed, cleaned of fatty tissue on a slab of dry ice, frozen in liquid nitrogen and stored in sealed plastic tubes at −30 °C. All rats were killed between 0900 and 1100h. The frozen adrenal glands were weighed before being homogenized, and noradrenaline, adrenaline, dopamine and DOPAC (dihydroxyphenyl acetic acid) concentrations in the homogenates were measured by high performance liquid chromatography with electrochemical detection according to Baksi et al (1981, 1985) and Baksi & Hughes (1982), with minor modification for the adrenal gland (Baksi & Hughes 1983, 1984). Recovery for all four compounds was 65–75%. The detection limit for noradrenaline, adrenaline and DOPAC was 6 ng, and for dopamine 1·5 ng. The data were statistically analysed by analysis of variance and the multiple range test (Duncan 1955).

Results

The results indicate that treatment with bromocriptine for 10 days (Fig. 1) significantly increased the adrenaline concentration in the adrenal glands in a dose-dependent manner. The increases in noradrenaline and dopamine were significant at the two higher doses of the drug. DOPAC was not detectable in any adrenal gland homogenate. The NA/DA ratio was not altered significantly by bromocriptine treatment, but A/NA ratios in the groups treated with 0·5 and 5·0 mg kg^{-1} of the drug were significantly higher compared with control of 0·05 mg kg^{-1} groups. The haloperidol-treated groups (Fig. 2), on the other hand, showed a biphasic effect on adrenal adrenaline concentration. Noradrenaline con-

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centration showed a significant increase only after the lowest dose of the drug. There was no difference in dopamine concentration as a result of haloperidol treatment nor were NA/DA or A/NA ratios significantly different.

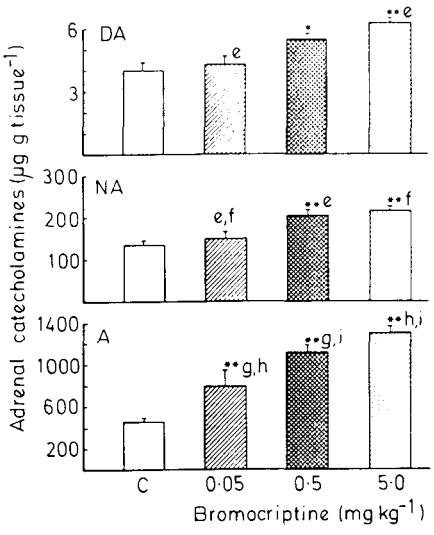

FIG. 1. Concentrations of dopamine (DA), noradrenaline (NA) and adrenaline (A) in the adrenal gland of rats treated with bromocriptine (mg kg^{-1} day^{-1}) for ten days. Values are mean ± s.e.m. of four rats. Significantly different *($P < 0.05$); **($P < 0.01$) from control (vehicle 1·0 mg kg^{-1}) group. Means bearing the same superscript are significantly ($P < 0.05$) different.

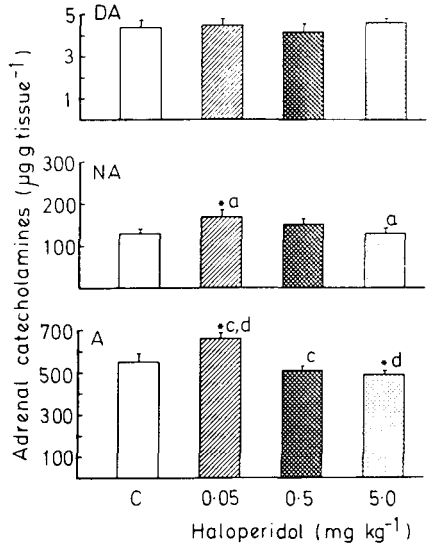

FIG. 2. Concentrations of dopamine (DA), noradrenaline (NA) and adrenaline (A) in the adrenal gland of rats treated with haloperidol (mg kg^{-1} day^{-1}) for ten days. Values are mean ± s.e.m. of four rats. Significantly different *($P < 0.05$) from control (vehicle 1·0 ml min^{-1}) group. Means bearing the same superscript are significantly ($P < 0.05$) different.

Discussion

This study shows that subchronic treatments with a dopamine agonist (bromocriptine) and antagonist (haloperidol) in male rats have different effects on adrenal catecholamines, particularly the dopamine concentration. Bromocriptine treatment in general increased noradrenaline, adrenaline and dopamine concentrations, but haloperidol did not alter dopamine concentration and had a biphasic effect on the adrenaline concentration. Whether dopamine synthesis and degradation were both increased after bromocriptine treatment is not known, because DOPAC, a major metabolite of dopamine, was not detected by us in adrenal homogenate using HPLC and electrochemical detection with a detection limit of 6 ng, while its contents in the gland is reported to be around 250 ng g^{-1} (Lackovic & Relja 1984). In the bromocriptine-treated groups (0·5 and 5·0 mg kg^{-1}), dopamine concentration (in μg g^{-1}) increased, but DOPAC remained undetected. The reason for this discrepancy is not known, although it is possible that dopamine was being converted preferentially to homovanillic acid (HVA), another of its metabolites, which was not extracted by the aluminum absorption process. Haloperidol blocks, whereas bromocriptine stimulates, dopamine receptors in the brain (Aghajanian & Bunny 1977; Dichiara et al 1978). It cannot be ascertained from the present preliminary study whether these two non-selective dopaminergic drugs had any effect on the dopamine receptors that may be present in the adrenal medulla. Moreover, the presence of specific dopaminergic receptors in the rat adrenal medulla is not definitely known, although Relja & Lackovic (1984) have evidence to support this. Dopaminergic receptors in the zona glomerulosa of the adrenal cortex have been identified (Dunn & Bosman 1981).

The ratio of NA/DA was not significantly affected by haloperidol treatment, indicating that noradrenaline synthesis from dopamine by the enzyme dopamine-β-hydroxylase (DH) was not affected. Similarly the A/NA ratio showed no significant change, indicating that the enzyme phenylethanolamine-*N*-methyl transferase (PNMT), which is essential for the synthesis of adrenaline from noradrenaline, was also not affected by haloperidol treatment. In the bromocriptine-treated groups only the A/NA ratio increased in a dose-dependent manner (data not shown), indicating that the enzyme PNMT was stimulated. It has been suggested that adrenomedullary dopamine content is an indicator of noradrenaline and adrenaline biosynthesis, reflecting changes in their turnover rate and tyrosine hydroxylase activity (Snider & Carlsson 1972). In our study, the increased dopamine concentration was also reflected in higher noradrenaline and adrenaline concentration in the adrenal gland of bromocriptine-treated groups

(Fig. 1). The lack of any alteration in the NA/DA ratio due to DA concentration and the increase in the A/NA ratio corresponding to an increase in dopamine level suggest that in the adrenal gland this is an indicator of adrenaline synthesis. Racz et al (1984) have also demonstrated a similar relation between dopamine and adrenaline in the bovine adrenal gland.

Although the drugs were injected daily for ten days, the catecholamines were measured 24 h after the last injection. In this situation our observation may represent a 'rebound' phenomenon for bromocriptine, which has a shorter half-life then haloperidol.

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Effect of fluoxetine pretreatment on the neurochemical changes induced by amfonelic acid combined with spiperone in rats

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Combined treatment with amfonelic acid plus spiperone caused large increases in 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) and a decrease in dopamine in rat striatum. 5-Hydroxytryptamine (5-HT) was decreased in striatum (but not in hypothalamus), and 5-hydroxyindoleacetic acid (5-HIAA) was increased in the striatum. Pretreatment with fluoxetine, an inhibitor of uptake into 5-HT neurons, antagonized the decrease in 5-HT and the increase in 5-HIAA and in the ratio 5-HIAA/5-HT but did not antagonize the changes in dopamine or its metabolites. The amfonelic acid–spiperone combination apparently causes increased release of dopamine in striatum, and the released dopamine is accumulated by 5-HT nerve terminals via the membrane uptake carrier. Inhibition of that carrier by fluoxetine prevents the release of 5-HT caused by the dopamine influx.

Amfonelic acid, a non-amphetamine stimulant drug, causes a large increase in dopamine turnover in rat striatum when given in combination with classical neuroleptic drugs (Shore 1976). Waldmeier (1985) recently reported that the massive release of dopamine that occurred when amfonelic acid and a neuroleptic drug were given in combination, resulted in the accumulation of dopamine by 5-HT-containing nerve terminals in rat striatum, leading to depletion of 5-HT. That depletion was antagonized by citalopram, an inhibitor of 5-HT uptake. Our experiments, undertaken to confirm and extend those observations, revealed (1) that the decrease in 5-HT was accompanied by an increase in 5-HIAA in the striata of rats given amfonelic acid plus spiperone and (2) that the increase in the ratio 5-HIAA/5-HT was antagonized by fluoxetine, a selective inhibitor of 5-HT uptake, which did not antagonize the changes in dopamine metabolism.

* Correspondence.

Method

Male Wistar rats (HSD/[WI]BR), about 150 g, obtained from Harlan Sprague-Dawley, Inc., Cumberland, Indiana, received injections of spiperone (0·5 mg kg^{-1} i.p.) 90 min before they were killed and 5 min after