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Influence of Apomorphine on Brain Serotonin Turnover Rate

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GRABOWSKA M. *Influence of apomorphine on brain serotonin turnover rate.* PHARMAC. BIOCHEM. BEHAV. 3(4) 589–591, 1975. – Apomorphine (5.0 mg/kg) accelerated the disappearance of 5-HIAA from the brain of pargyline-pretreated rats as well as depletion of brain 5-HT caused by inhibition of its synthesis. The latter effect has been abolished by spiroperidol. The results obtained suggest that apomorphine increases the 5-HT turnover rate, secondary to the stimulation of central dopamine receptors.

Apomorphine Brain 5-HT turnover

IN previous studies from this laboratory apomorphine, regarded as a central dopamine receptor stimulating agent [2,3], has been found to elevate the concentration of main serotonin (5-HT) metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in rat and mouse brain [5,7]. These findings were confirmed recently, by Scheel-Krüger and Hasselager [11].

The above mentioned biochemical changes, which have been noted in whole brain as well as in discrete rat brain structures [5,7], may be an indication of increased turnover of brain 5-HT under the influence of apomorphine.

The present study was aimed to find further data confirming the influence of apomorphine on turnover rate of 5-HT in rat brain.

METHOD

The turnover rate of brain 5-HT was calcualted from the rate of decline of 5-HIAA in brain after inactivation of MAO by pargyline [13] and from the rate of depletion of brain 5-HT when its synthesis was blocked by α-propyldopacetamid [1].

Animals

Wistar male rats, weighing 120–170 g, were used. The spectrofluorometrical determination of 5-HT and 5-HIAA in the total rat brain were performed according to Maickel *et al.* [9] and Miller *et al.* [10] respectively.

Procedure

The rats were decapitated at 30 min interval after pargyline (75 mg/kg IP) or 3–4 hr after α-propyldopacetamid (H 22/54, 500 mg/kg IP) administration. Apomorphine hydrochloride (5.0 mg/kg) was injected subcutaneously 45 min before pargyline or decapitation (in experiments with H 22/54).

Apomorphine hydrochloride (McFarlane), pargyline hydrochloride (VEB Magdeburg), α-propyldopacetamid (AB Hassle) and spiroperidol (Janssen) were injected as saline solutions or suspension with 3% tween 80 in a volume of 4.0 ml/kg.

RESULTS

The control level of 5-HIAA in rat brain was 542 ng/g ± 21 and no changes under the influence of apomorphine in the experiment presented were observed.

After the injection of pargyline the 5-HIAA level declined (Fig. 1). The rate of 5-HT synthesis, calculated from the rate constant of 5-HIAA loss and the normal 5-HIAA level [13] was 239 ng/g/h; turnover time of 5-HT was 135 min.

The values obtained from the slope of decline of 5-HIAA after pretreatment with apomorphine were 382 ng/g/h and 86 min respectively.

H 22/54 reduced the brain 5-HT level (Table 1); the effect of the drug was more pronounced 4 hr after injection.

With the dose of apomorphine used there was significant potentiation in the degree of 5-HT depletion resulting from H 22/54 administration. In normal rats apomorphine increased the brain 5-HT level or did not change it.

Spiroperidol (0.5 mg/kg) did not affect the level of brain 5-HT in rats pretreated with H 22/54. At the same time the

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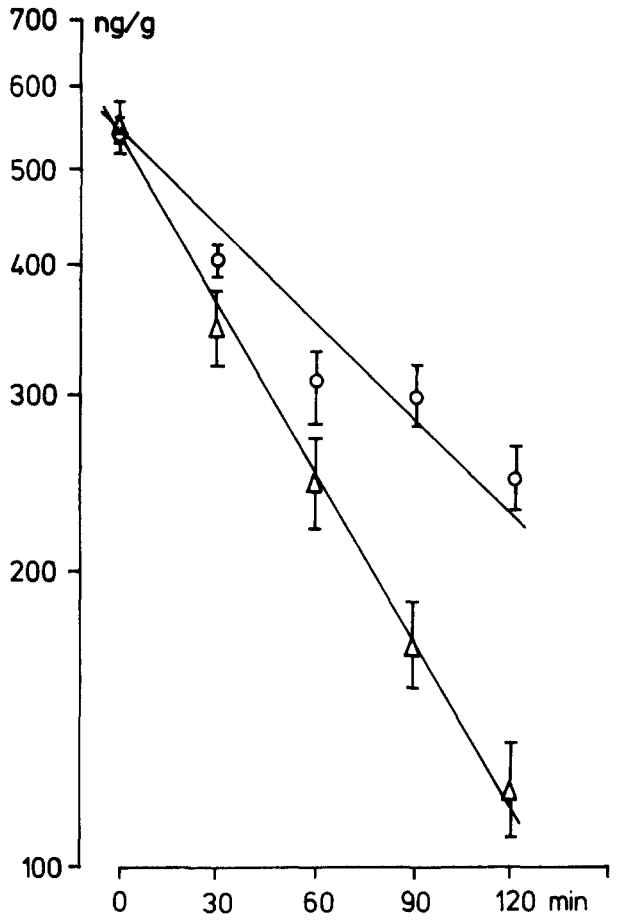

FIG. 1. Time study of level of 5-HIAA in rat brain after injection of pargyline (○——○) or pargyline and apomorphine (△——△). Each point is the average ± S. E. M. of 6–8 determinations.

TABLE 1

THE INFLUENCE OF APOMORPHINE ON BRAIN 5-HT CONCENTRATION IN NORMAL AND H 22/54 PRETREATED RATS

Drug Treatment (mg/kg)	5-HT ng/g ± SEM
Saline	615.3 ± 15.1
Apomorphine 5.0[a]	732.9 ± 23.0‡
H 22/54 500[a,c]	570.0 ± 11.9*
H 22/54 500 + apomorphine 5.0[b]	477.1 ± 19.9†
Saline	554.3 ± 25.1
Apomorphine 5.0[a]	532.9 ± 23.0 N.S.
H 22/54 500[a,d]	360.3 ± 9.0‡
H 22/54 500 + apomorphine 5.0[b]	317.9 ± 7.1†
H 22/54 500 + spiroperidol 0.5[b]	348.0 ± 13.1 N.S.
H 22/54 500 + spiroperidol 0.5 + apomorphine 5.0[b]	356.2 ± 9.0 N.S.

*$p<0.05$ †$p<0.01$ ‡$p<0.001$
[a]Comparison with saline-treated group
[b]Comparison with H 22/54-treated group
[c]H 22/54 injected 3 hr before decapitation
[d]H 22/54 injected 4 hr before decapitation
Each group consisted of 7–8 animals. Statistical significance was evaluated with student's *t* test.

drug counteracted the depletion of 5-HT caused by apomorphine (Table 1).

DISCUSSION

Apomorphine did not change the level of brain 5-HT or increased it. At the same time the drug has been found to accelerate the depletion of 5-HT caused by inhibition of its synthesis. This finding may indicate the increased utilization of brain 5-HT under the influence of apomorphine.

In about 85 percent of previously described experiments [5] the increase of 5-HIAA level resulting from apomorphine administration had been noted. No changes in the level of this metabolite were observed in the remaining experiments as well as in those presented here. The decline of 5-HIAA after inhibition of MAO activity was, however, more rapid in rats pretreated with apomorphine.

Our previous suggestion concerning the influence of apomorphine on brain 5-HT turnover seems to be confirmed by present results. The increased utilization of 5-HT under the influence of apomorphine can be concluded both, from acceleration of dissapearance of 5-HT when its synthesis was blocked as well as from more rapid decline of 5-HIAA after MAO blockade, even if we consider all reservations concerning the methods applied here.

The described apomorphine induced biochemical changes could result partly from increased supply of tryptophan to the brain. According to Tagliamonte *et al.* [12] the level of brain tryptophan was not changed after apomorphine administration.

It is generally accepted that apomorphine exerts its central action by stimulation of dopamine receptor [2,3]. The influence of apomorphine on serotoninergic neurons, which seems to affect the pharmacological action of the drug [4, 6, 7], can be secondary effect, resulting from primary stimulation of dopamine structures. It is supported by fact that acceleration of depletion of brain 5-HT caused by apomorphine in H 22/54 pretreated rats was abolished by spiroperidol. It has been found previously that apomorphine induced changes in brain 5-HT and 5-HIAA concentrations were prevented by pretreatment with butyrophenones, drugs regarded as blockers of central dopamine receptors [5]. The possibility of direct influence of apomorphine on serotonin neurons cannot be excluded. Dopamine injected into the raphe system produced cortical synchronization in cats and this effect has been blocked by haloperidol [8].

REFERENCES

1. Andèn, N. -E., H. Corrodi and K. Fuxe. Hallucinogenic drugs of the indolealkylamine type and central monoamine neurons. *J. Pharmac. exp. Ther.* **179:** 236–249, 1971.
2. Andèn, N. -E., A. Rubenson, K. Fuxe and T. Hökfelt. Evidence for dopamine receptor stimulation by apomorphine. *J. Pharm. Pharmac.* **19:** 627–629, 1967.
3. Ernst, A. M. Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats. *Psychopharmacologia* **10:** 316–323, 1967.
4. Grabowska, M. Influence of midbrain raphé lesion on some pharmacological and biochemical effects of apomorphine in rats. *Psychopharmacologia,* in press.
5. Grabowska, M., L. Antkiewicz, J. Maj and J. Michaluk. Apomorphine and central serotonin neurons. *Pol. J. pharmac. pharm.* **25:** 29–39, 1973.
6. Grabowska, M. and J. Michaluk. On the role of serotonin in apomorphine-induced locomotor stimulation in rats. *Pharmac. Biochem. Behav.* **2:** 263–265, 1974.
7. Grabowska, M., J. Michaluk and L. Antkiewicz. Possible involvement of brain serotonin in apomorphine-induced hypothermia. *Eur. J. Pharmac.* **23:** 82–89, 1973.
8. Kostowski, W. and S. Gumulka. Injections of some drugs affecting cholinergic and catecholaminergic neurons into the pontine raphe area: effects on EEG pattern. *Pol. J. pharmac. Pharm.* **26:** 351–368, 1974.
9. Maickel, R. P., R. H. Cox, Jr., J. Saillant and F. P. Miller. A method for the determination of serotonin and norepinephrine in discrete areas of rat brain. *Int. J. Neuropharmac.* **7:** 275–281, 1968.
10. Miller, F. P., R. H. Cox, W. R. Snodgrass and R. P. Maickel. Comparative effects of p-chlorophenylalanine, p-chloroamphetamine and p-chloro-N-methylamphetamine on rat brain norepinephrine, serotonin and 5-hydroxyindole-3-acetic acid. *Biochem. Pharmac.* **19:** 435–442, 1970.
11. Scheel-Krüger, J. and E. Hasselager. Studies of various amphetamines, apomorphine and clonidine on body temperature and brain 5-hydroxytryptamime metabolism in rats. *Psychopharmacologia* **36:** 189–202, 1974.
12. Tagliamonte, A., P. Tagliamonte, J. Perez-Cruet, S. Stern and G. L. Gessa. Effect of psychotropic drugs on tryptophan concentration in the rat brain. *J. Pharm. exp. Ther.* **177:** 475–480, 1971.
13. Tozer, T. N., N. H. Neff and B. B. Brodie. Application of steady state kinetics to the synthesis rate and turnover time of serotonin in the brain of normal and reserpine-treated rats. *J. Pharm. exp. Ther.* **153:** 177–182, 1966.