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# Papaverine, Drug-Induced Stereotypy and Catalepsy and Biogenic Amines in the Brain of the Rat

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KOSTOWSKI, W., S. GAJEWSKA, A. BIDZINSKI AND M. HAUPTMAN. *Papaverine, drug-induced stereotypy and catalepsy and biogenic amines in the brain of the rat.* PHARMAC. BIOCHEM. BEHAV. 5(1) 15–17, 1976. – The effects of papaverine on haloperidol-induced catalepsy and apomorphine-induced stereotypy as well as brain monoamines concentrations in rats were studied. Papaverine increased cataleptogenic effect of haloperidol whilst reduced stereotypy induced by apomorphine. Slight but significant decrease in brain dopamine concentration was observed in rats treated with papaverine. The present study indicates that papaverine has influences upon dopaminergic mechanisms in the brain.

Papaverine and C.N.S. Catalepsy Brain monoamines Stereotypy

PAPAVERINE has been shown to be a potent inhibitor of phosphodiesterase in brain and other tissues [12]. Recent findings have indicated that dopamine (DA) and dopamine-like compound, apomorphine (AP) stimulated the adenyl-cyclase activity in the striatum [9,13]. These findings led to the hypothesis that adenyl-cyclase may function as a DA receptor in some brain areas [9,13]. It has been suggested that tetrahydropapaveroline, the compound structurally similar to papaverine may be an important metabolite of DA [12,15]. Thus, the close relations between papaverine and dopaminergic brain mechanisms may exist. To check this possibility we decided to determine this effect of papaverine on DA – related motor disturbances induced by some psychotropic compounds. The phenothiazine and butyrophenone cataleptic agents are considered to exert their effects by interruption of dopaminergic function via DA receptors blockade [8,14] whilst stereotypy induced by amphetamines and apomorphine is mainly related to excitement of pre- and postsynaptic dopaminergic mechanisms [2, 5, 14].

## METHOD

Wistar male rats weighing 180–200 g housed in macrolon cages at 20–22°C and fed normal diet were used. Cataleptogenic effect of haloperidol and intensity of stereotypy induced by apomorphine were scored according to the method described previously by us [6]. To investigate the effects of papaverine on brain monoamine concentrations, rats were treated with 5.0 mg/kg IP of this drug and killed by decapitation after 150 min. Their brains were rapidly removed and serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA) and catecholamines (DA and noradrenaline, NA) were fluorimetrically estimated in the whole brain (except for the cerebellum). The extractions of brain amines and 5-HIAA prior to spectrofluorimetry was carried out according to the procedure of Haubrich and Denzer [7] with slight modifications. Brain tissue was homogenated with 15 ml of acidified butanol. The homogenate was centrifuged for 15 min at 15 000 xg and 2.5 ml aliquots of the supernatant were shaken with 5.0 ml of heptane and 1.2 ml of 0.1 N HCl. Internal standards were introduced at this point. After centrifugation the amines were determined directly in the acid phase, DA and NA – by iodine oxidation according to Chang [3] and 5-HT by condensation with o-phtaldialdehyde according to Maickel *et al.* [11]. 5-HIAA remaining after the first extraction in the organic phase, was extracted into 0.8 ml of 0.5 M phosphate buffer (pH 7.4) and determined according to the procedure described by Korf *et al.* [10].

Drugs used were: Haloperidol (Janssen), Papaverinum hydrochloricum (POLFA) and Apomorphinum hydrochloricum (dissolved in 0.9% saline and injected IP in the volume of 0.1–0.2 ml).

## RESULTS AND DISCUSSION

Papaverine given in the doses of 2.5 mg/kg and 5.0 mg/kg IP failed to change the general behavior of rats. This drug, however markedly potentiated catalepsy induced by haloperidol (0.15 mg/kg IP). When papaverine was given 60 min before, the cataleptogenic effect of neuroleptic was potentiated (increase of the score) and prolonged (Table 1).

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Stereotypy induced by apomorphine (4 mg/kg IP) was slightly decreased and shortened when animals were pretreated 60 min before with 5.0 mg/kg of papaverine (Table 2). Biochemical analysis showed decreased concentration of brain DA but other amines and 5-HIAA remained unchanged (Table 3). Our data indicate that action of drugs such as neuroleptics and DA-like stimulants may be changed by papaverine. Central effects of papaverine were poorly investigated. This drug is known to influence on sleep cycle in rats [1] but no effects on brain 5-HT and NA were observed.

Recently, two classes of DA receptors have been recognized within the striatum: excitatory and inhibitory [4]. In this context, the role of DA and dopaminergic receptors seems to be more complex and different receptors are believed to be stimulated or blocked by different drugs [4]. Our studies provide the evidence that papaverine and haloperidol may act upon the same functional unit whilst apomorphine (being only poorly affected by papaverine) may attack different sites. The decreased DA concentration in brains of rats treated with papverine is difficult to explain and further experiments including DA turnover and metabolite measurements are needed.

TABLE 1

PAPAVERINE AND CATALEPSY INDUCED BY HALOPERIDOL IN RATS

| Experimental Group | N | Intensity of catalepsy (scored) after: 30 min | 60 min | 90 min | 2 hr | 150 min | 3 hr |
|---|---|---|---|---|---|---|---|
| Control | 24 | 9.0 | 9.9 | 9.6 | 9.8 | 9.2 | 8.5 |
| Papaverine | | | | | | | |
| 2.5 mg/kg | 10 | 10.3 NS | 12.0* | 13.2‡ | 13.0‡ | 12.6† | 12.5† |
| 5.0 mg/kg | 12 | 12.6‡ | 12.8‡ | 13.0‡ | 12.9† | 13.0‡ | 12.7‡ |

Control group received 0.2 ml of 0.9% NaCl. Haloperidol was injected (0.15 mg/ kg i.p.) 60 min after papaverine.
*$p<0.05$.
† = $p<0.001$.
‡ = $p<0.001$ (according to $\chi^2$ test). N—number of rats. NS—not significant.

TABLE 2

PAPAVERINE AND APOMORPHINE-INDUCED STEREOTYPY IN RATS

| Experimental Group | N | Intensity of stereotypy (scored) after: 15 min | 30 min | 45 min | 60 min | 75 min | 90 min | 105 min |
|---|---|---|---|---|---|---|---|---|
| Control | 10 | 3.37 | 4.40 | 4.65 | 4.65 | 4.40 | 2.85 | 0.30 |
| Papaverine 5.0 mg/kg | 10 | 3.55 NS | 4.15 NS | 4.65 NS | 4.30 NS | 3.20 $p<0.05$ | 1.35 $p<0.05$ | 0.15 NS |

For explanations see Table 1. Apomorphine (4 mg/kg IP) was injected 60 min after papaverine.

TABLE 3

EFFECTS OF PAPAVERINE ON MONOAMINES AND 5-HIAA CONCENTRATIONS IN THE RAT BRAIN

| Experimental Group | N | Content in brain, ng/g SE: Serotonin | 5-HIAA | Noradrenaline | Dopamine |
|---|---|---|---|---|---|
| Control | 7 | 710.2 ± 96.6 | 490.0 ± 73.6 | 471.7 ± 44.0 | 2027.0 ± 231.0 |
| Papaverine 5 mg/kg | 7 | 762.4 ± 93.0 NS | 442.8 ± 58.8 NS | 462.2 ± 37.4 NS | 1591.0 ± 359.0 $t = 2.50$ $p<0.05$ |

Control group received 0.2 ml of 0.9% NaCl. Animals were killed 150 min after injections. For statistical analysis the Student's $t$-test was used.

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