Pharmacology Biochemistry & Behavior, Vol 10, pp 475–480 Printed in the U S A

Potentiation of Haloperidol-Induced Catalepsy by Dopamine Agonists: Possible Involvement of Central 5-Hydroxytryptamine[1,2]

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(Received 9 January 1978)

CARTER, C J AND C J PYCOCK *Potentiation of haloperidol catalepsy by dopamine agonists possible involvement of central 5-hydroxytryptamine* PHARMAC BIOCHEM BEHAV 10(4) 475–480, 1979 —Apomorphine (0 12–2 mg/kg, SC) and *d*-amphetamine (1–8 mg/kg, IP) were each able, at certain doses, to potentiate the cataleptic state produced by the neuroleptic agent, haloperidol (1 mg/kg, IP) In subsequent biochemical experiments, in which the effects of combinations of apomorphine or *d*-amphetamine and haloperidol on brain monoamine levels were studied, this behavioural observation was seen to be related to an enhanced utilisation of 5-hydroxytryptamine (5-HT) in certain brain regions The results suggest not only the possible involvement of 5-HT in the production of catalepsy, but also that the effects of these 'classical' dopamine agonists on other central transmitter systems should be considered when interpreting their various behavioural responses

Dopamine agonists Catalepsy Haloperidol Mesolimbic 5-Hydroxytryptamine

NEUROLEPTIC-induced catalepsy is primarily associated with dopamine receptor blockade in mesolimbic and extrapyramidal regions of the brain While a distinct site of action for the production of this response has not been, and probably cannot be, forwarded, there is a growing weight of evidence to suggest that the antipsychotic potential of the neuroleptics may be related more specifically to the consequences of dopamine receptor blockade in mesolimbic regions [7,8]. Neuroleptic catalepsy can be influenced by modifying central 5-hydroxytryptamine (serotonin, 5-HT) function For example, we have recently shown that neuroleptic catalepsy can be potentiated by facilitating 5-HT transmission [3], while conversely blockade of central 5-HT mechanisms either by lesion techniques or drugs will have the reverse effect [6, 16, 18].

While the effects of dopamine receptor antagonism result in the state of catalepsy, dopamine receptor agonists produce stereotyped behavioural responses which, paradoxically, may also to some extent be dependent upon raised 5-HT transmission [5,23] The 'stereotypic' agents are usually regarded as pure dopamine agonists, although their probable direct interaction with other neurotransmitter systems cannot be overlooked. For example, amphetamine is also known to be capable of releasing 5-HT [12] and apomorphine has been reported as enhancing cerebral 5-HT utilisation [13,15] as well as causing a weak inhibition of 5-HT uptake [19] In view of the effects of these agents on 5-HT transmission, and a possible role of 5-HT in neuroleptic-induced catalepsy, we have investigated the effects of *d*-amphetamine and apomorphine on the cataleptic response produced by haloperidol. In addition, we have attempted to correlate the behavioural results with biochemical changes, and have investigated the concentrations of 5-HT and its metabolite 5-hydroxyindole acetic acid (5-HIAA) in dopamine containing regions of the brain after a combination of apomorphine or *d*-amphetamine with haloperidol

METHOD

Behavioural Measurements

Male Porton rats weighing 200–250 g were used in all experiments Catalepsy was defined as the ability of an animal to maintain an abnormal position or posture, and was assessed by placing the forelimbs over a horizontal bar 10 cm above the floor of the cage· the intensity of catalepsy was related to the time that this position was maintained. The time was converted to the numerical scoring system adopted by Costall and Olley [10], where no catalepsy, score 0; 0 1–2 5 min, score 1; 2.6–5.0 min, score 2, 5 1–10 0 min, score 3; 10 1–20 min, score 4, 20 1–∞, score 5 Catalepsy was assessed one hour after injection of haloperidol (1 mg/kg, IP) The effect of *d*-amphetamine (range 1–8 mg/kg, IP, 5 min

[1]This work was supported by the Medical Research Council

[2]Thanks are due to Mrs Shirley Burns for expert technical assistance We are also grateful to Smith, Kline & French and to Searle Laboratories for generous supplies of dexamphetamine and haloperidol respectively

after haloperidol) or apomorphine (range 0.12–2 mg/kg, SC, 30 min after haloperidol) on haloperidol-induced catalepsy was determined Saline was used as a control injection instead of the dopamine agonists

Biochemical Assessments

The effect of a combination of haloperidol and the dopamine agonists on regional 5-HT turnover was investigated Two methods were employed to assess 5-HT utilisation—one being a study of the ratio of 5-HIAA 5-HT concentrations [2], and the other to measure 5-HIAA levels in probenecid-treated rats (Probenecid is an agent used to block the efflux of neurotransmitters and their metabolites from the brain and the subsequent build-up of metabolites is taken as an index of transmitter turnover, and is regularly applied to monitor 5-HT turnover [20])

In the first series of experiments *d*-amphetamine (range 1–8 mg/kg, IP) or apomorphine (range 0 12–2 mg/kg, SC) was administered at 5 or 30 min respectively to haloperidol (1 mg/kg, IP) or saline pretreated rats. Animals were killed 1 hr after neuroleptic administration for the regional assessment of 5-HT and 5-HIAA concentrations In the second series of experiments the same drug combinations were used except that each animal received additionally probenecid (200 mg/kg, IP) 35 min after neuroleptic administration, and animals were killed 30 min later

Rats were killed by cervical dislocation, the brain removed and dissected over ice into 4 regions, comprising the striatum (caudate nucleus/putamen), nucleus accumbens septi, tuberculum olfactorium, and frontal cortex Approximately 1 mm thick sections were taken from the frontal cortical region, and the tuberculum olfactorium removed from the ventral surface. A vertical cut was made in the forebrain, and the tissue in the proximity of the anterior commissure was punched out with reference to the atlas of Pellegrino and Cushman [21] and taken as the nucleus accumbens region, distinguishing it from the more dorsally and caudally located striatal area The striata were dissected out from the remaining tissue Brain regions from both sides of the brain were pooled, weighed and homogenised in acidified butanol for the extraction of biogenic amines After centrifugation, 5-HT and 5-HIAA were determined fluorimetrically following condensation with *o*-phthaldialdehyde [11], while dopamine was assayed by the method of Laverty and Sharman [17] Prior to assay, dopamine was purified on alumina yielding a 63–68% recovery· concentrations stated represent uncorrected values

Drugs

Dexamphetamine sulphate (Smith, Kline and French) was dissolved in 0 9% saline Apomorphine hydrochloride (MacFarlan-Smith) was dissolved in 0.1% nitrogen-bubbled sodium metabisulphite solution, and haloperidol (Searle) in 1% acetic acid Probenecid (Sigma) was dissolved in a minimum amount of 0 5 N NaOH made up to volume with distilled water. All doses refer to the salt, and all drugs were injected in a volume of 1 mg/ml

Statistics

At least 6 rats were used at each dose level for behavioural and biochemical measurements and the results are expressed as the mean ± the standard error of the mean. For the behavioural data, the significance values of difference between control and drug-treated groups were computed using a Mann-Whitney U test for non-parametric data Significance of differences of biochemical data were calculated using the Student's *t* test Statistical significance was taken at the level $p<0$ 05

RESULTS

Behavioural Observations

Haloperidol, at a dose of 1 mg/kg, produced a reproduceable cataleptic response with a mean score of approximately 2 (range of scores 1–3), one hour after injection The simultaneous injection of *d*-amphetamine (1–8 mg/kg) had little effect on this score at the 1 and 2 mg/kg dose However, the 4 mg/kg dose of *d*-amphetamine produced a significant potentiation of the neuroleptic induced catalepsy ($p<0$ 05) (Fig. 1) The higher dose of *d*-amphetamine (8 mg/kg) resulted in stereotyped sniffing and licking behaviour which antagonised the cataleptic response in some rats

A similar pattern was observed following the administration of apomorphine (0 12–2 mg/kg) 30 min after haloperidol pretreatment The lower doses of apomorphine produced little change in haloperidol-induced catalepsy, while the 0.5 mg/kg dose significantly potentiated the cataleptic response ($p<0.05$) (Fig. 1) The higher doses of apomorphine (1 and 2 mg/kg) reduced the cataleptic effects of haloperidol ($p<0$ 05 at 2 mg/kg), as the animals displayed varying degrees of stereotyped behaviour

Biochemical Results

The effects of haloperidol together with a combination of either apomorphine or *d*-amphetamine on regional concentrations of 5-HT, 5-HIAA and dopamine were assessed in normal rats Alone neither apomorphine (0 12–2 mg/kg, 30 min) nor *d*-amphetamine (1–8 mg/kg, 1 hr) caused any significant changes in either 5-HT or 5-HIAA levels measured in the nucleus accumbens, tuberculum olfactorium, striatum or cortex (results not shown) Similarly, administration of a single dose of haloperidol (1 mg/kg) resulted in no significant changes in the concentrations of 5-HT or 5-HIAA in any of the brain regions studied (Fig 2)

The combination of haloperidol and apomorphine resulted in significant increase in 5-HIAA concentrations in the nucleus accumbens in a dose-related manner for the 0 25–1 mg/kg doses of apomorphine ($p<0$ 05) (Fig 2) In addition the haloperidol—2 mg/kg apomorphine combination caused increased 5-HT levels in the nucleus accumbens The haloperidol-apomorphine combination also significantly elevated striatal 5-HIAA levels at the 0 5 and 1 mg/kg dose of apomorphine ($p<0$ 05) and striatal 5-HT concentrations at the 0 5 mg/kg dose of apomorphine ($p<0$ 05) (Fig 2). No statistically significant changes in indoleamine concentrations were recorded in either tuberculum olfactorium or cortex

The effect of the combination of haloperidol and *d*-amphetamine on accumbens and striatal 5-HT and 5-HIAA concentrations is also shown in Fig 2 *d*-Amphetamine (2 and 4 mg/kg) in combination with haloperidol significantly elevated accumbens 5-HIAA concentrations ($p<0$ 05) without significant changes in 5-HT levels The highest dose of amphetamine (8 mg/kg) significantly decreased accumbens 5-HT concentrations ($p<0$ 05), having no effect on accumbens 5-HIAA levels In the striatum only the 4 mg/kg

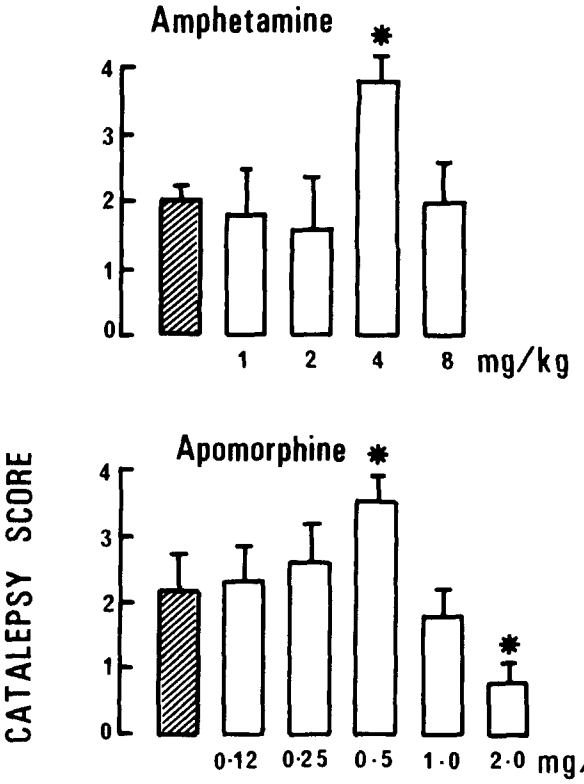

FIG 1 The effects of *d*-amphetamine (1–8 mg/kg, IP), and apomorphine (0 12–2 0 mg/kg, SC) on the cataleptic state induced in rats by haloperidol (1 mg/kg, IP) *d*-Amphetamine was administered 5 min after, and apomorphine 30 min after haloperidol injection The hatched columns represent control catalepsy scores in animals injected with haloperidol alone Each column is the mean of 6 determinations, the vertical bars represent standard error values, and the asterisks denote significance values of $p<0$ 05 (Mann-Whitney U test)

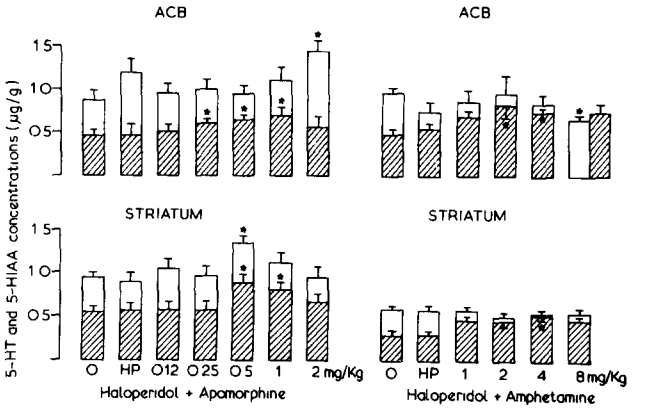

FIG 2 The effects of haloperidol (HP) (1 mg/kg, IP, 1 hr) and combinations of apomorphine (0 12–2 mg/kg, SC, 30 min) and haloperidol (left-hand side) and of *d*-amphetamine (1–8 mg/kg, IP, 1 hr) and haloperidol (right-hand side) on concentrations of 5-HT (open columns) and 5-HIAA (hatched columns) in nucleus accumbens (ACB) and striatum of rat brain Each column is the mean of 6 determinations vertical bars indicate standard errors *Denotes statistical significance at the level $p<0$ 05 (Student's *t* test) (No significant changes in either 5-HT or 5-HIAA concentrations were recorded in either tuberculum olfactorium or cortex following any of the drug combinations)

d-amphetamine/haloperidol combination had any significant biochemical effect, causing an increase in 5-HIAA concentrations ($p<0.05$) (Fig 2) None of the *d*-amphetamine/haloperidol combinations had any significant effect on tuberculum olfactorium or cortical indoleamine concentrations

None of the drugs tested nor the relevant combinations caused any significant changes in the dopamine concentrations of the nucleus accumbens (control 5 81 ± 0 70 μg/g wet weight tissue), tuberculum olfactorium (4 92 ± 0.87 μg/g), or striatum (6.63 ± 1 01 μg/g)

The effect of a combination of haloperidol and dopamine agonists on regional 5-HIAA concentrations in probenecid-treated rats is shown in Tables 1 and 2. The only significant change in metabolite levels seen following *d*-amphetamine alone (4 mg/kg) was a 19% increase in tuberculum olfactory 5-HIAA ($p<0$ 05) (Table 1) No changes were seen following haloperidol alone Combinations of these two drugs elevated 5-HIAA concentrations in tuberculum olfactorium at the 2, 4 and 8 mg/kg doses of amphetamine ($p<0$ 05, $p<0$ 01), in the nucleus accumbens at the 4 mg/kg dose, and in the striatum at the 4 and 8 mg/kg doses of amphetamine ($p<0$ 05) when compared to control animals (Table 1) These probenecid results indicate an increased 5-HT utilisation following the haloperidol-amphetamine combination. Because a significant increase in 5-HIAA levels was seen in the tuberculum olfactorium following *d*-amphetamine alone, the biggest overall increase in metabolite concentrations, when compared with either haloperidol-amphetamine, or *d*-amphetamine alone were associated with the striatal and nucleus accumbens regions No significant changes in cortical 5-HIAA concentrations were recorded following any of the drug combinations (results not shown)

In the parallel experiment, apomorphine alone had no effect on 5-HIAA concentrations in tuberculum olfactorium, nucleus accumbens or striatum (Table 2) With the combination of haloperidol and apomorphine, the only changes recorded were in nucleus accumbens and striatum at the 1 and 2 mg/kg dose level of apomorphine, when both doses significantly elevated 5-HIAA concentrations at both sites ($p<0.05$, $p<0$ 01) (Table 2). No significant changes were observed in cortical 5-HIAA levels (results not shown)

DISCUSSION

The states of catalepsy and stereotypy seem to represent two opposing behavioural parameters, revolving around the functional state of forebrain dopamine systems It is not surprising therefore that cateleptic agents can reverse the behavioural effects of stereotypic agents, and vice versa For example, it is well documented that neuroleptic drugs block hyperactive and stereotyped responses produced by amphetamine and apomorphine [9,22], while classical 'stereotypic' agents can reverse the cataleptic states induced by the phenothiazenes and butyrophenones. Indeed, in our own studies, higher doses of *d*-amphetamine and apomorphine were able to reduce the cataleptic effects of haloperidol

TABLE 1

EFFECT OF THE COMBINATION OF HALOPERIDOL AND D-AMPHETAMINE ON REGIONAL CEREBRAL 5-HIAA CONCENTRATIONS IN PROBENECID-TREATED RATS

Drug	Brain Region		
	Tuberculum olfactorium	Nucleus accumbens	Striatum
control	1 24 ± 0 07	0 75 ± 0 04	0 65 ± 0 03
HP	1 33 ± 0 10	0 78 ± 0 04	0 70 ± 0 04
HP+amphet (1 mg/kg)	1 42 ± 0 10	0 76 ± 0 10	0 63 ± 0 05
HP+amphet (2 mg/kg)	1 45 ± 0 04*	0 82 ± 0 04	0 62 ± 0 09
HP+amphet (4 mg/kg)	1 61 ± 0 08*'†'	0 89 ± 0 05*†‡	0 78 ± 0 05*‡
HP+amphet (8 mg/kg)	1 53 ± 0 15*	0 83 ± 0 04	0 81 ± 0 06*†‡
amphet (4 mg/kg)	1 48 ± 0 09*	0 76 ± 0 02	0 62 ± 0 04

Rats were given haloperidol (HP) (1 mg/kg, IP) or saline at time zero followed 5 min later by *d*-amphetamine (amphet) (range 1–8 mg/kg, IP) or saline All animals received probenecid (200 mg/kg, IP) at 30 min and were subsequently killed at 1 hr for the determination of regional 5-HIAA concentrations 5-HIAA concentration is expressed as μg/g wet weight tissue ± 1 SEM Each result is the mean of 6 determinations

*=significant difference between drug group and saline control, $p<0$ 05, *'$p<0$ 01

†=significant difference between drug group and HP alone, $p<0$ 05, †'$p<0$ 01

‡=significant difference between drug group and amphet alone, $p<0$ 05 (Student's *t* test)

However, the surprising paradoxical potentiation of haloperidol-induced catalepsy by these two classical dopamine agonists does not allow interpretation solely in terms of postsynaptic dopamine receptor stimulation or antagonism In view of the reported functional relationship between manipulation of central 5-HT mechanisms and neuroleptic-induced catalepsy and an apparent serotoninergic component of the classical 'stereotypic' drugs (see Introduction) we investigated the possible involvement of 5-HT in the interaction observed with the dopamine agonists apomorphine and *d*-amphetamine

The ratio of 5-HIAA 5-HT is taken as an index of 5-HT turnover [2] and the changes in concentrations of its metabolite 5-HIAA indicate the level of 5-HT utilisation [20]. In our

TABLE 2

EFFECT OF THE COMBINATION OF HALOPERIDOL AND APOMORPHINE ON REGIONAL CEREBRAL 5-HIAA CONCENTRATIONS IN PROBENCID-TREATED RATS

Drug	Brain Region		
	Tuberculum olfactorium	Nucleus accumbens	Striatum
Control	1 45 ± 0 07	0 98 ± 0 05	0 82 ± 0 07
HP	1 53 ± 0 13	0 89 ± 0 07	0 97 ± 0 13
HP+apo (0 25 mg/kg)	1 36 ± 0 14	1 01 ± 0 09	0 87 ± 0 05
HP+apo (0 5 mg/kg)	1 44 ± 0 08	1 10 ± 0 10	0 99 ± 0 09
HP+apo (1 mg/kg)	1 55 ± 0 16	1 24 ± 0 09*†'‡	1 34 ± 0 09*'†‡'
HP+apo (2 mg/kg)	1 56 ± 0 12	1 20 ± 0 10*†‡	1 42 ± 0 13*'†‡'
apo (1 mg/kg)	1 62 ± 0 11	0 86 ± 0 09	0 77 ± 0 08

Rats were given haloperidol (HP) (1 mg/kg IP) or saline at time zero followed 30 min later by apomorphine (apo) (range 0 25–2 mg/kg, SC) or saline All animals received probenecid (200 mg/kg, IP) 5 min after apomorphine and were subsequently killed 30 min later for the determination of regional 5-HIAA concentrations 5-HIAA concentration is expressed as μg/g wet weight tissue ± 1 SEM Each result is the mean of 7 or 8 determinations Numbers in parenthesis after apo indicate dose

*=significant difference between drug group and saline control, $p<0$ 05, *'$p<0$ 01

†=significant difference between drug group and HP alone, $p<0$ 05, †'$p<0$ 01

‡=significant difference between drug group and apo alone, $p<0$ 05, ‡'$p<0$ 01 (Student's *t* test)

system neither the dopamine antagonist (haloperidol) nor the dopamine agonists (apomorphine and *d*-amphetamine) at the doses and times employed significantly altered 5-HT utilisation and turnover (although an increase in 5-HIAA concentration within the tuberculum olfactorium was measured after 4 mg/kg *d*-amphetamine) However, both combinations of dopamine agonist and neuroleptic significantly potentiated cerebral 5-HT utilisation There is a possible parallel connection between the potentiation of haloperidol catalepsy by apomorphine and *d*-amphetamine and the effects of these drug combinations on regional 5-HT turnover. Certainly there is a significant potentiation of 5-HT utilisation at the 0 5 mg/kg dose of apomorphine and 4 mg/kg dose of *d*-amphetamine indicating a fair correlation between behavioural and biochemical states Presumably the reversal of the cataleptic effect by the higher doses of dopamine agonists is the result of increasing dopamine receptor stimulation with concomitant displacement of haloperidol, as 5-HT function remains elevated

It is difficult to select an anatomical site at which these effects may be mediated, although it is tempting to suggest the nucleus accumbens or striatum as the prime candidate, as the biochemical changes in these nuclei more closely follow the behavioural patterns observed Indeed, the nucleus accumbens has already been strongly implicated as an important site of action of agents with antipsychotic potential [8,9], while striatal dysfunction is known to be associated with parkinsonism, and laboratory models of catalepsy In addition, in separate lesion studies where we have selectively lesioned 5-HT terminals in dopamine-terminal regions, 5-HT depletion within the nucleus accumbens produces a large reduction in the cataleptic potential of the neuroleptic agent fluphenazine [4]

Apomorphine or amphetamine alone, at the doses used in this study, had little effect on central 5-HT turnover It is possible that blockade of their main effects on the postsynaptic dopamine receptor by the neuroleptics, which themselves have been reported to enhance central 5-HT turnover or utilisation [14,24], allows the subsequent manifestation, and measurement of their actions on serotonergic systems

The potentiation of haloperidol-induced catalepsy by amphetamine or apomorphine thus appears to be related to an increase in central 5-HT utilisation. Whether this is an indirect result of their effects on presynaptic or autoregulatory dopamine receptors [1] or related to an additional pharmacological action of these drugs on the serotonergic system is unknown Although these agents can be regarded as potent dopamine agonists, some of their behavioural effects—particularly stereotyped behaviour, have also been shown to depend upon central 5-HT mechanisms [5]. This dependence may reflect hitherto unconsidered actions of drugs such as amphetamine and apomorphine on these systems.

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