Blockade of dopamine receptors explains the lack of 5-HT stereotypy on treatment with the putative 5-HT\textsubscript{1A} agonist LY165163

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Abstract. The putative serotonin (5-HT)\textsubscript{1A} agonist 1-[2-(4-aminophenyl)ethyl]-4-(3-trifluormethylphenyl) piperazine (LY165163, PAPP) induces hyperphagia and hypothermia in rats, but unlike other 5-HT agonists, does not induce 5-HT stereotypy even at high doses (10 mg/kg sc). LY165163 (1 mg/kg) increased striatal DOPA accumulation in animals treated with the aromatic amino acid decarboxylase inhibitor 3-hydroxy-benzylhydrazine (NSD 1015) (100 mg/kg ip). This increase was also found when the drug was given to animals pretreated with parachlorophenylalanine (pCPA) (150 mg/kg ip daily for 3 days). LY165163 (2 and 4 mg/kg sc) inhibited stereotyped behaviour induced by the dopamine (DA) agonist apomorphine (2 mg/kg sc). LY165163 (2, 4, 10 mg/kg sc) also inhibited stereotyped components of the 5-HT syndrome induced by 5-methoxy-N,N-dimethylyptamine (5-MeODMT; 5 mg/kg ip) which previous studies (e.g. Andrews et al. 1982) suggested to require DA (head weaving, reciprocal forepaw treading). Thus, while other 5-HT\textsubscript{1A} agonists such as 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) cause stereotypy, this does not occur with LY165163, probably because the drug blocks DA receptors.

Key words: LY165163 – Stereotypy – pCPA – 5-MeODMT, Apomorphine – Serotonin – Dopamine – 5-HT\textsubscript{1A} agonists – Rat
induced stereotypy, animals were given LY165163 (1, 2, 4, 10 mg/kg sc) and behaviour recorded over its complete time course (90 min). Apomorphine (2 mg/kg sc) only caused a slight increase in duration of gnawing in the present study and the difference from vehicle-treated controls was not significant. The most marked behavioural change caused by apomorphine at this dose was a significant increase in rearing and sniffing. Apomorphine also increased the duration of locomotion but the difference was not significant. Pretreatment with LY165163 (2 mg/kg, 4 mg/kg) significantly reduced the duration of rearing and stereotypy.

Biochemical analysis. Animals were given daily injections of pCPA (150 mg/kg ip) or 0.9% NaCl, 72, 48 and 24 h before injection of LY165163 (1 mg/kg sc) or saline. Thirty minutes later the aromatic amino acid decarboxylase inhibitor NSD 1015 was injected (100 mg/kg ip). After an additional 30 min the animals were decapitated, their brains removed and the striatum separated from the rest of the brain.

The above brain regions were homogenised in 0.4 M perchloric acid containing 0.1% sodium metabisulphite, 0.01% EDTA, 0.1% cysteine and centrifuged at 3000 g for 20 min. A sample of supernatant was then filtered through a 0.45 μm filter (Millipore Ltd.) and 14% v/v methanol, pH 2.75. This was filtered through an A lexultrasp t column (4.6 mm × 7.5 cm) (Beckman Ltd.) was used. The mobile phase was 0.1 M phosphate, 0.0035% EDTA, 0.016% octyl sodium sulphate and 14% v/v methanol, pH 2.75. This was filtered through a 0.2 μm cellulose nitrate filter (Millipore Ltd., London) and degassed with helium before use. The electrochemical detector was an ESA Coulochem model 5100A (Severn Analytical Ltd) with a dual electrode analytical cell (model 5011). Electrode 1 was set at −0.04 V and electrode 2 at +0.35 V with respect to palladium reference electrodes.

Behavioural analysis. Behavioural testing was conducted using individual Perspex cages (25 × 25 × 21 cm) with grid floors. Animals were taken from their home cages and placed in the Perspex cages 5 min before drug treatment. Wood blocks were placed on the grid floor in order to investigate drug-induced gnawing. Behaviour was recorded on videotape. All experiments were conducted between 1000 and 1700 hours. At the end of each observation period, animals were returned to their home cages. Each animal was tested once only.

To investigate the effects of LY165163 on apomorphine-induced stereotypy, animals were given LY165163 (1, 2, or 4 mg/kg sc) or 0.9% NaCl 30 min before apomorphine (2 mg/kg sc) and behaviour recorded over its complete time course (90 min).

To assess the effects of LY165163 on 5-MeODMT-induced stereotypy, animals were given LY165163 (1, 2, 4, 10 mg/kg) or 0.9% NaCl 30 min before 5-MeODMT (5 mg/kg ip) and behaviour recorded over its complete time course (30 min).

The videotape recordings were analysed using a Sharp MZ80B microcomputer and a modification of the “BASIC” Ethol program described by Hendrie and Bennett (1983). The experimenter analysed the behaviour of each animal by typing two letter codes on the computer keyboard which indicated various components of motor and stereotyped behaviour. Once any code had been typed the experimenter did not press any other key until the indicated behaviour ended. The “Return” key was then pressed which caused the program to record the duration, frequency and latency to onset of the behaviour. At the end of the observation period, the command “End” caused the computer to print out frequency, duration and latency for each behaviour. If behavioural components of interest occurred concurrently, the videotape was re-run to permit further scoring.

In the present study, the following behavioural components were scored: feeding, drinking, inactivity, locomotion, grooming and rearing. Components of the 5-HT behavioural syndrome were also scored, i.e. forepaw treading, flat body posture, hindlimb abduction or stretching, head weaving and “wet dog shakes”.

Statistics. The biochemical data were analysed by independent Student t tests. The behavioural data were analysed by one way analysis of variance (ANOVA). Where ANOVA yielded a significant result (P<0.05), between group comparisons were made using Dunnett’s test and Student’s t test where appropriate.

Results

Table 1 shows that LY165163 (1 mg/kg sc) significantly increased the accumulation of DOPA in the striatum after treatment with the aromatic amino acid decarboxylase inhibitor NSD 1015 (100 mg/kg ip). The relative increase in the rest of the brain was smaller and did not reach significance. Rats pretreated with pCPA (150 mg/kg, 72, 48, 24 h) showed smaller increases of DOPA after treatment with NSD 1015 but the additional increase in the striatum of animals also given LY165163 was proportionate to that found in the absence of pCPA treatment. The corresponding DOPA values in the rest of brain appeared unaffected by LY165163. Treatment with LY165163 also decreased 5-HTP accumulation in brains of saline-treated animals. However 5-HTP accumulation was not evident after pCPA treatment (data not shown).

Table 2 shows the effects of pretreatment with saline or LY165163 (1, 2, 4 mg/kg sc) on the duration of locomotion and components of apomorphine-induced stereotypy (2 mg/kg sc) in a 90-min test period. Apomorphine (2 mg/kg sc) only caused a slight increase in duration of gnawing in the present study and the difference from vehicle-treated controls was not significant. The most marked behavioural change caused by apomorphine at this dose was a significant increase in rearing and sniffing. Apomorphine also increased the duration of locomotion but the difference was not significant. Pretreatment with LY165163 (2 mg/kg, 4 mg/kg) significantly reduced the duration of rearing and stereotypy.