Original Investigations

Neuroleptic Properties of cis-N-(1-Benzyl-2-methylpyrroloidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (YM-09151-2) with Selective Antidopaminergic Activity

Shinji Usuda, Koji Nishikori, Osamu Noshiro, and Hiroo Maeno

Department of Pharmacology and Biochemistry, Central Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd. No. 1-8, Azusawa-1-Chome, Itabashi-Ku, Tokyo 174, Japan

Abstract. A new benzamide, cis-N-(1-benzyl-2-methylpyrroloidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (YM-09151-2) exhibited more potent and longer-lasting inhibitory effects on apomorphine-induced behaviours (stereotyped behaviour, emesis and hypothermia), and methamphetamine-induced stereotyped behaviour, conditioned avoidance response and open field behaviour than either structurally similar benzamides (YM-0850 and sulpiride) or classical neuroleptics [chlorpromazine (CPZ) and haloperidol (HPD)]. Such inhibitory effects of YM-09151-2 relative to cataleptogenicity were greater than those of CPZ and HPD. In contrast, sulpiride elicited few of the neuroleptic effects described above. YM-09151-2, a potent inhibitor for dopamine-sensitive adenylate cyclase (Ki: 3.0 nM) reduced, in a selective manner, the binding of [3H]dopamine to the dopamine D1 receptor (Ki: 4.8 nM) associated with adenylate cyclase rather than to the dopamine D2 receptor (Ki: 0.98 μM) independent of adenylate cyclase. Sulpiride, on the contrary, inhibited only the binding to the dopamine D2 receptor. CPZ and HPD antagonized [3H]dopamine non-selectively at the two distinct dopaminergic receptors. These results suggest that YM-09151-2 is a potent and long-lasting neuroleptic with a highly selective blocking action on the dopamine D1 receptor.

Key words: 3-Pyrroloidinylbenzamide – YM-09151-2 – Neuroleptic – Dopaminergic blockade – D1 and D2 receptors

Introduction

Neuroleptic drugs which are currently employed for the management of schizophrenia are structurally classified into phenothiazines, thioxanthenes, butyrophenones, diphenylbutylpiperidines and dibenzodiazepines. In addition, some benzamide derivatives such as sulpiride and metoclopramide have recently been reported to possess antipsychotic effects (Borenstein et al. 1968; Toru et al. 1972; Stanley et al. 1979), although their clinical efficacy is relatively weak as compared to that of classical neuroleptics such as phenothiazines and butyrophenones. These benzamides elicit few neuroleptic effects and no inhibition of dopamine-sensitive adenylate cyclase but are potent inhibitors of emesis in animals (Laville and Margarit 1969; Costall et al. 1978; Jenner et al. 1978).

However, since our recent discovery of YM-08050, a benzamide derivative with potent neuroleptic effects in animals and a strong inhibitory effect on dopamine-sensitive adenylyl cyclase (Usuda et al. 1979), such pharmacological and biochemical properties are no longer characteristic of all of the benzamide derivatives. Very recently, another new benzamide derivative, cis-N-(1-benzyl-2-methylpyrroloidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (YM-09151-2) (Fig. 1) with a methyl group at position 2 on the pyrroloidyl ring of YM-08050 has been reported to exhibit more potent anti-apomorphine effects (Iwanami et al. 1980). In the present studies, YM-09151-2 is compared to YM-08050, sulpiride, haloperidol (HPD) and chlorpromazine (CPZ) in a variety of neuroleptic tests in animals as well as in antagonistic effects at the dopamine receptors.

Materials and Methods

Drugs

YM-09151-2, YM-08050, sulpiride and apomorphine hydrochloride were synthesized in our laboratories. The following drugs were commercially obtained: haloperidol (Dott. Bonapace & C.), chlorpromazine hydrochloride (Rhone-Poulenc), methamphetamine hydrochloride (Dainippon), [3H]dopamine (New England Nuclear) and dopamine hydrochloride (Sigma Chemical). After dissolving in 1 N HCl, YM-09151-2, YM-08050 and sulpiride were all diluted with distilled water and used after adjustment of the pH to 4 with sodium bicarbonate. Haloperidol was dissolved in a few drops of lactic acid with subsequent dilution with distilled water. Chlorpromazine hydrochloride was dissolved in distilled water.

Animals

Male ICR mice (28 – 31 g), male Wistar rats (260 – 300 g) and mongrel dogs of either sex (11 – 14 kg) were used. The animals were given free access to food and water with a 12-h light-dark cycle (lights on 7 AM). Behavioral studies were started at 9 – 10 AM.

Statistics

The method of Litchfield and Wilcoxon (1949) was used in determining the half-maximal effective dose (ED50) and evaluating statistically.

Fig. 1. Chemical structure of cis-N-(1-benzyl-2-methylpyrroloidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (YM-09151-2)
parallelism between the dose-response curves of YM-09151-2 and other drugs tested. The ED_{50} value was calculated using three or more doses of the test drugs. The avoidance response rate was evaluated statistically by Student's t-test.

Apopomorphine-Induced Stereotyped Behaviour in Rats

The method of Janssen et al. (1965) was utilized with a slight modification. The rats were observed in individual cages (21 x 21 x 17 cm) with clear plastic walls. A dose of 1.25 mg/kg of apomorphine was injected intravenously into the rats 30 min after subcutaneous administration of test drugs. Inhibitory effects of the drugs on the stereotyped behaviour were judged to be positive unless both gnawing and licking behaviours were observed for the period of 20 min after apomorphine-injection. A group of six to ten rats at each dose level was used to determine the dose required to inhibit stereotyped behaviour by 50% (ED_{50}).

Apopomorphine-Induced Emesis in Dogs

The dogs were fasted 180 min before subcutaneous administration of test drugs. Apomorphine at 0.1 mg/kg which induced emesis in all of the control dogs was given subcutaneously 30 min after the administration of drugs. Apomorphine-induced emesis in dogs required to inhibit stereotyped behaviour by 50% (ED_{50}).

Apopomorphine-Induced Stereotyped Behaviour in Rats

Methamphetamine-Induced Stereotyped Behaviour in Rats

The rats were observed in individual cages as described in the apomorphine-induced stereotyped behaviour test. Test drugs were injected subcutaneously 30 min before the intraperitoneal administration of methamphetamine (5 mg/kg). Inhibitory effects of test drugs were judged to be positive unless the stereotyped behaviour as characterized by ambulation and rearing was observed essentially according to Hall (1934). A cataleptic response was judged to be positive when the front paws of the rats remained on a bar 7 cm above the bench for more than 30 s. The ED_{50} was defined as the dose required to induce catalepsy in 50% of the rats when tested 30 min after the subcutaneous administration of the test drug. Groups of six to eight rats were used at each dose level.

Apopomorphine-Induced Hypothermia in Mice

Groups of four mice were housed in plastic cages (12 x 17 x 24 cm) in a temperature-controlled room at 23 ± 1 °C for 1 h prior to the measurement of rectal temperature with a thermometer (Nihon-Kohden). Test drugs were administered to mice 30 min before the subcutaneous administration of apomorphine and the differences (ΔT) in the temperature immediately before, and 30 min after, apomorphine administration, were calculated. The ED_{50}, the dose which reduced by 50% the mean ΔT of a submaximal dose of apomorphine, 0.2 mg/kg, was obtained using eight to twelve mice for each dose of the test drug.

Methamphetamine-Induced Stereotyped Behaviour in Rats

The rats were trained to avoid an electroshock (unconditioned stimulus) by pressing a lever during buzzing and light (conditioned stimuli) in an open field apparatus which was enclosed in a ventilated sound-proof chamber. The conditioned stimuli for 5 s preceded a 5 s unconditioned stimulus (electroshocks of 0.4–0.6 mA delivered through a scrambler to the grid floor) with the intertrial interval of 25 s. The rats that failed to respond within 5 s from the onset of unconditioned stimulus were scored as an escape failure. The rats received 2-h trials daily for at least 20 consecutive days. The animals which exhibited at least 90% avoidance response for a further 2 consecutive days were subjected to the efficacy test of the drugs. The rats were given the drugs subcutaneously after 1-h training trials (pre-drug level) and subsequently subjected to the next 3-h test trials. When the avoidance response was found to be still strongly suppressed at the end of the test trials, the 20-min trials were further conducted every hour until their avoidance response returned to the pre-drug level. The drugs were given at intervals of at least 10–11 days. Avoidance and escape responses were recorded and summed at 20 min intervals. The mean avoidance response per 20 min was plotted against time. The ED_{50} in this experiment was defined as the dose required to reduce by 50% the pre-drug avoidance response during a 60-min period, between 30 and 90 min after subcutaneous administration of the test drug. Groups of six to eight rats were used for each dose level.

Apopomorphine-Induced Stereotyped Behaviour in Rats


dopamine).