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Interactions of Apomorphine and a Novel Neuroleptic Dibenzodioxazocine Derivative, as Evidenced by Changes of Somato-autonomic Reflexes and Spontaneous Sympathetic Activity in Cats

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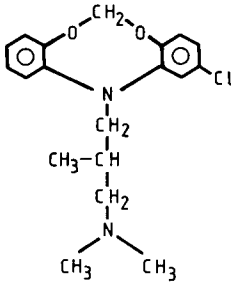
Abstract—The apomorphine-antagonistic effects of EGYT-2509, a novel neuroleptic compound, has been studied by two different methods suitable for investigating the dopaminergic modulation of sympathetic output. (1) In cats lightly anaesthetized with urethane (600 mg kg^{-1} i.p.), blood pressure (BP) reflexes evoked by electrical stimulation of the sciatic nerve were inhibited by apomorphine (0·2 mg kg^{-1} i.v.) at low frequencies of stimuli (2–8 Hz), while the BP reflexes were facilitated by apomorphine at higher frequencies of stimulation; the evoked contractions of the nictitating membrane were depressed in the entire range of frequencies applied. EGYT-2509 (1·5 mg kg^{-1} i.v.) antagonized both the inhibition and facilitation of pressor reflexes induced by apomorphine. EGYT-2509, given alone, in doses exceeding 1·5 mg kg^{-1} either did not influence or inhibited the responses of nictitating membrane and of BP; the inhibition could be antagonized by haloperidol. The apomorphine-induced sustained hypotension was inhibited by EGYT-2509 (18·5 mg kg^{-1}): after EGYT-2509, higher doses of apomorphine (0·7 vs 0·2 mg kg^{-1}) were required for the effect. Sustained hypotension could be elicited by EGYT-2509, too; after apomorphine, smaller doses of EGYT-2509 (8·5 vs 18·5 mg kg^{-1}) were enough to decrease BP. (2) In cats anaesthetized with chloralose and urethane (50 and 400 mg kg^{-1} i.p., respectively), apomorphine (0·2 mg kg^{-1}) inhibited the spontaneous activity of the postganglionic renal sympathetic nerve. EGYT-2509 (< 1 mg kg^{-1}) and chlorpromazine (0·2–0·5 mg kg^{-1}) failed to antagonize the apomorphine-induced inhibition. Haloperidol (0·4 mg kg^{-1}), however, restored the renal nerve activity. All three compounds, EGYT-2509, chlorpromazine and haloperidol, themselves, inhibited the sympathetic discharges. The results indicate that EGYT-2509, in addition to its potent anti-apomorphine activity, possesses some apomorphine-like features, too.

Recently, a series of neuroleptic dibenzodioxazocine derivatives, resembling some phenothiazines in structure, has been developed (Petöcz et al 1985). Detailed pharmacological studies of a representative of this group, EGYT-2509 [(±)-2-chloro-12*H*-12-(3-dimethylamino-2-methyl-propyl)-dibenzo [d,g][1,3,6]dioxazocine hydrochloride] (I) revealed specific dopamine-antagonistic activity with potentially minimal undesirable side effects (Gyüre et al 1985; Petöcz et al 1985; Gacsályi et al 1987).

In the effects of neuroleptics, their interaction with dopamine-mediated neurotransmission plays a highly relevant role (Carlsson 1978; Creese et al 1978; Robertson & MacDonald 1986).



I. Structure of EGYT-2509

Dopaminergic mechanisms are involved in the integration of the sympathetic output (Dóda & György 1982, 1985; Jadhav et al 1983). We therefore chose two different approaches to study dopaminergic influence of the sympathetic outflow and the antidopaminergic action of EGYT-2509 thereon. Firstly, the use of somato-autonomic reflexes as a test procedure proved to be a suitable tool (Baum & Shropshire 1977; Dóda et al 1977; Walland 1978) to investigate the effects of various compounds upon the efferent sympathetic activity. In urethane-anaesthetized and immobilized cats, electrical stimulation of the sciatic nerve elicits pressor reactions and contractions of the nictitating membrane (Molnár et al 1969). The amplitude of the responses depends on the frequency of the stimuli applied (voltage and duration kept constant). Various drugs influence the evoked reactions in different ways (Dóda et al 1977; Koltai et al 1978; Dóda & György 1982), the effects of dopaminergic agonists are highly characteristic (Dóda & György 1982). They depress nictitating membrane reflexes in the entire range of the stimulation frequencies applied. At the same time, blood pressure (BP) reflexes are depressed by dopaminergic agonists only in the lower frequency range (1–4 Hz). They are, however, potentiated at higher rates (32–128 Hz). Secondly, we applied direct recording of the spontaneous activity of renal sympathetic postganglionic efferent fibres; dopaminergic agonists depress the activity of both the pre- and postganglionic ones (Jadhav et al 1983; Dóda & György 1985).

The aim of the present paper was to investigate the action of EGYT-2509 on the effects of apomorphine upon somato-autonomic reflexes and spontaneous renal sympathetic nerve activity.

Materials and Methods

Somato-autonomic reflexes

Cats of either sex, 2·5–3·5 kg (n = 38) were anaesthetized with urethane (600 mg kg^{-1} i.p.), immobilized with gallamine triethiodide (5 mg kg^{-1} i.v.) and artificially ventilated. Supplementary doses of gallamine were given as required. The trachea, and the left femoral artery and vein were cannulated. The right sciatic nerve was dissected and mounted on bipolar platinum electrodes. BP was measured from the femoral artery by means of a Statham P 23 Db transducer connected to a Hellige electromanometer. Contractions of the nictitating membrane were recorded by means of a force-displacement transducer (Biegestab N Type 355, Hugo Sachs Elektronik). BP and membrane contractions were recorded on a Hellige polygraph. The sciatic nerve was stimulated with trains of square-wave pulses of 0·3ms duration, and of 16V intensity for 2s (Electrostimulator, Type 4767, MEDICOR). The frequency of stimulation was varied from 2 to 128Hz, in a logarithmically increasing sequence. The experiments began 30–40 min after finishing the preparatory procedure: control frequency-response curves were obtained two or three times; stimuli were delivered after steady state conditions had been established following the administration of various drugs.

Spontaneous renal nerve activity

Cats of either sex, 3·0–4·5 kg (n = 26) were anaesthetized with a mixture of chloralose and urethane (50 and 400 mg kg^{-1} i.p., respectively). One of the left renal nerve trunks was dissected free, sectioned near the kidney and placed on bipolar platinum electrodes. The nerve was kept under warm liquid paraffin. Electrical activity was amplified with a differential amplifier (MIKI, Type 1623E), displayed on a Tektronix dual beam storage oscilloscope; the output of the amplifier was also led into an analogue integrator (NOVA GMK, Hungary). The integrator was reset automatically to zero every 2 or 5 s. The output of the integrator was recorded on a multichannel direct writing device (Hellige).

Drugs and statistical analysis

The drugs used were: apomorphine HCl (Alkaloida), α-chloralose (Fluka), chlorpromazine HCl (EGIS Pharmaceuticals), EGYT-2509 (EGIS Pharmaceuticals), gallamine triethiodide (Flaxedil, Spécia), haloperidol (Gedeon Richter), urethane (Reanal). All drugs, except the anaesthetics, were given intravenously.

Student's *t*-test was used for statistical analyses.

Results

Effect of EGYT-2509 on somato-autonomic reflexes

Intravenous administration of EGYT-2509 (0·5–18·5 mg kg^{-1} cumulative) caused a dose-dependent transient (1–3 min) depressor effect (Table 1) followed by a moderate (20–30 mmHg) hypertension that lasted for 20–30 min. In response to higher doses, however, only hypotension could be observed. In experiments where apomorphine (0·2 mg kg^{-1}) had been given, the effect of EGYT-2509 was the same, with the exception that even a lower dose of the latter (8·5 mg kg^{-1}) was enough to elicit long lasting hypotension. Pretreatment of the animals with EGYT-2509 did not influence the apomorphine induced depressor effect, but higher doses of the latter (0·7 mg kg^{-1}) were needed to evoke a sustained hypotension.

Table 1. Short lasting (1–3 min) depressor effects of EGYT-2509.

Dose mg kg^{-1} i.v., cumulative	Decrease of blood pressure mmHg, mean ± s.e.m.	n
0·5	16·1 ± 2·0	11
1·5	30·5 ± 2·4	11
3·5	45·5 ± 3·9	11
8·5	61·5 ± 5·1	10
18·5	72·9 ± 4·7	7

The tone of the nictitating membrane was not influenced by the doses of EGYT-2509 studied (Fig. 1).

EGYT-2509 in cumulative doses of more than 1·5 mg kg^{-1} did not influence or inhibit the pressor responses elicited by sciatic nerve stimulation. At a dose of 18·5 mg kg^{-1} however, only inhibition could be observed (Table 2A, Fig. 1). The evoked contractions of the nictitating membrane were also depressed by EGYT-2509 (Table 2B, Fig. 1). Haloperidol, in a dose (0·2 mg kg^{-1}) used to inhibit BP- and the membrane-reflexes, partially antagonized the inhibitory effects of EGYT-2509 (Fig. 1).

Effects of EGYT-2509 on apomorphine-induced changes in somato-autonomic reflexes

The characteristic effects of apomorphine (0·2 mg kg^{-1}) on pressor responses elicited by sciatic nerve stimulation (see introduction) were antagonized by EGYT-2509 in a dose of 1·5 mg kg^{-1} (Fig. 2A), higher doses of the drug (up to 8·5 mg kg^{-1}) depressed the responses in the entire range of frequencies applied.

The apomorphine-induced inhibition of the evoked contractions of the nictitating membrane were not antagonized by EGYT-2509 (1·5 mg kg^{-1}; Fig. 2B). Larger doses of EGYT-2509 led to a stronger inhibition of the reflexes. This inhibition seen in animals pretreated with apomorphine could be attenuated by haloperidol (0·2 mg kg^{-1}).

Haloperidol antagonized the apomorphine-induced changes of reflexes in a dose of 0·05 mg kg^{-1}, on increasing its dose (0·2 mg kg^{-1}) inhibition of the membrane reflexes ensued.

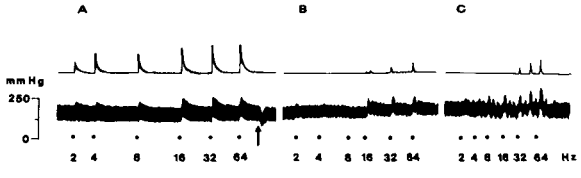


FIG. 1. Inhibitory effect of EGYT-2509 (18·0 mg kg^{-1} i.v., cumulative) on the reflexes of nictitating membrane (upper record) and blood pressure (lower record) elicited by electrical stimulation of the sciatic nerve in a cat anaesthetized with urethane (600 mg kg^{-1} i.p.) and the effect of haloperidol (0·2 mg kg^{-1} i.v.) thereon. Parameters of stimulations: 16 V, 0·3 ms, 2 s long trains, frequencies in Hz as indicated. A: control; B: after the administration of EGYT-2509 (the first 1 mg kg^{-1} dose at the arrow); C: after consecutive administration of haloperidol. Time lapse between A and B: 110 min, between B and C: 60 min.

Table 2. Pressor reflexes and contractions of the nictitating membrane elicited by sciatic nerve stimulations of various frequencies in cats anaesthetized with urethane (600 mg kg^{-1} i.p.) and the effect of EGYT-2509 thereon. Results are expressed in per cent of the stimulation-induced maximal effect of the individual animal, mean values ± s.e.m. (n = 6), *P < 0·05, **P < 0·01.

EGYT-2509 mg kg^{-1} i.v. cumulative	Stimulation frequency (Hz)						
	2	4	8	16	32	64	128
(A) Blood pressure							
Control	26·3 ± 12·5	24·3 ± 16·4	34·5 ± 16·1	59·7 ± 11·8	73·0 ± 14·0	88·0 ± 6·9	81·5 ± 8·4
0·5	14·3 ± 9·6*	46·0 ± 16·9	49·0 ± 22·9	38·0 ± 14·9	50·5 ± 17·3	81·7 ± 6·8	63·2 ± 17·3
1·5	7·2 ± 8·6*	48·5 ± 29·5	42·2 ± 20·4	24·2 ± 21·6	60·0 ± 13·9	78·8 ± 3·4	60·3 ± 26·8
3·5	1·5 ± 5·4*	27·8 ± 19·6	44·8 ± 8·5	52·0 ± 10·7	36·3 ± 15·1	64·3 ± 8·2	72·7 ± 15·6
8·5	3·0 ± 4·6*	1·7 ± 1·7*	23·5 ± 11·5	20·7 ± 10·8*	33·0 ± 12·7*	52·2 ± 21·3	44·5 ± 20·5
18·5	1·3 ± 1·3*	4·5 ± 7·0	15·8 ± 8·6	32·0 ± 6·5**	39·3 ± 14·8	45·5 ± 11·6*	44·8 ± 9·8*
(B) Nictitating membrane							
Control	56·5 ± 15·2	58·8 ± 19·3	56·8 ± 14·4	65·2 ± 13·7	78·1 ± 9·4	92·7 ± 5·0	89·0 ± 7·9
0·5	41·7 ± 16·1*	61·3 ± 16·7	66·3 ± 14·9	68·2 ± 15·2	69·3 ± 13·2	78·5 ± 9·5	58·2 ± 17·8
1·5	26·5 ± 11·5**	47·2 ± 13·0	49·8 ± 16·5	46·3 ± 16·6**	68·0 ± 12·2	85·8 ± 9·7	58·0 ± 14·4
3·5	8·8 ± 5·6**	23·0 ± 9·4*	37·0 ± 15·1	50·0 ± 12·4	45·7 ± 14·6	64·8 ± 17·2	40·2 ± 15·5*
8·5	4·2 ± 4·2**	2·3 ± 1·2*	19·8 ± 7·1*	22·0 ± 8·6**	33·8 ± 11·5*	31·0 ± 12·0**	24·3 ± 11·1**

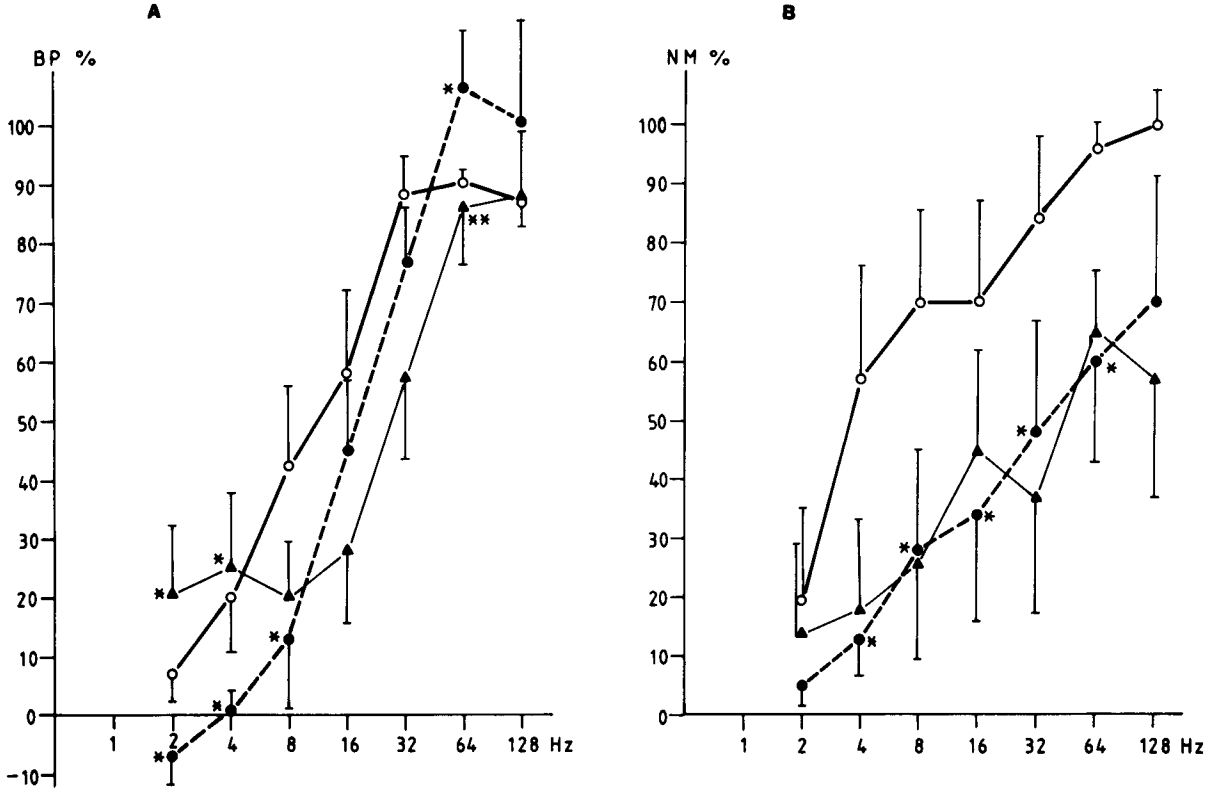


FIG. 2. The effect of EGYT-2509 on the apomorphine-induced alterations in the frequency characteristics of blood pressure (A) and nictitating membrane (B) reflexes elicited by electrical stimulation of sciatic nerve in cats anaesthetized with urethane (600 mg kg^{-1} i.p.). Mean values ± s.e.m. (n = 6) calculated from the amplitude of responses expressed in per cent of the maximal effect measured in the individual animals. Symbols: ○, control; ●, after 0·2 mg kg^{-1} i.v., apomorphine; ▲, after 1·5 mg kg^{-1} i.v., EGYT-2509. Effects of apomorphine are compared with the control, while those of EGYT-2509 are compared with apomorphine; significance levels: * P < 0·05; ** P < 0·02. Stimulation parameters as in Fig. 1.

Effects of EGYT-2509 on renal nerve activity

The spontaneous activity of the postganglionic renal sympathetic efferents was not influenced by 0·2–0·7 mg kg^{-1} EGYT-2509, higher doses of the drug induced inhibition (Fig. 3).

Effects of EGYT-2509 on apomorphine-induced inhibition of renal sympathetic nerve activity

Apomorphine (0·2 mg kg^{-1}) inhibited the spontaneous activity of the postganglionic renal sympathetic efferent fibres. EGYT-2509 did not antagonize the apomorphine-

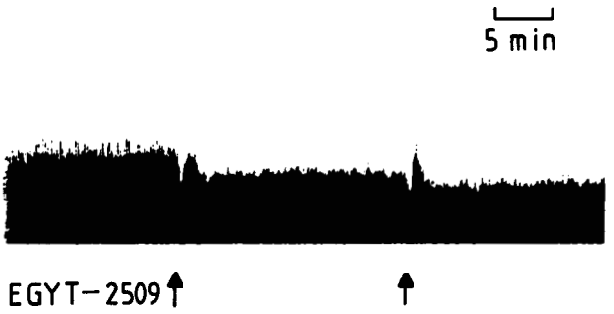


FIG. 3. EGYT-2509-induced inhibition of the spontaneous renal sympathetic nerve activity in a cat anaesthetized with chloralose and urethane (50 and 400 mg kg^{-1} i.p., respectively), demonstrated by a typical integrated record. Before the first arrow: control; arrows: administration of EGYT-2509 (1·0 and 2·0 mg kg^{-1} i.v., respectively).

induced inhibition. Moreover, in doses of 1·0 mg kg^{-1} or more it elicited further gradual diminution of sympathetic nerve activity (Fig. 4A).

Chlorpromazine, also, in doses of 0·2–0·7 mg kg^{-1} failed to antagonize the apomorphine-induced inhibition of sympathetic nerve activity and higher doses of the drug caused even deeper inhibition (Fig. 4B). Lower doses of chlorpromazine (0·1–0·2 mg kg^{-1}), given alone, did not influence the activity. Higher doses (0·5–2·0 mg kg^{-1}), however, depressed

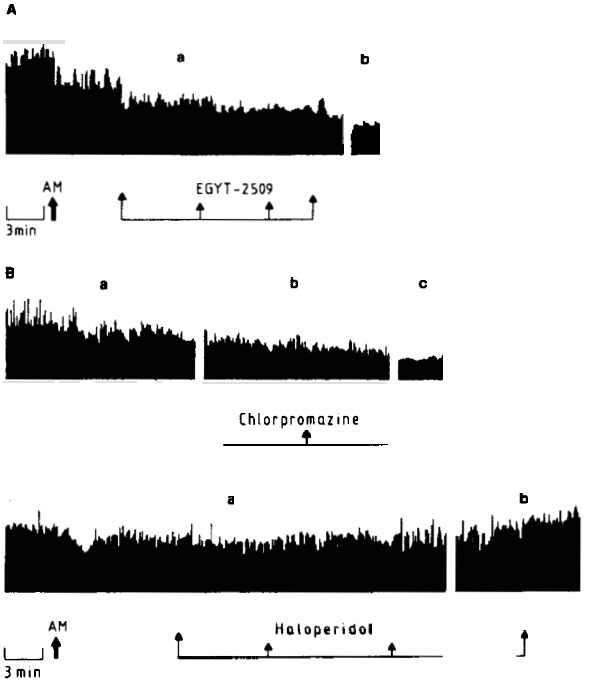


FIG. 4. The effect of EGYT-2509 (A), chlorpromazine (B) and haloperidol (C) on the apomorphine-induced inhibition of the spontaneous renal sympathetic nerve activity (integrated records) in three cats (A, B, and C, respectively) anaesthetized with chloralose and urethane (50 and 400 mg kg^{-1} i.p., respectively). Before the first arrows: controls; doses administered intravenously at the arrows: apomorphine (AM)—0·2 mg kg^{-1} EGYT-2509—0·2, 0·5, 1·0, and 2·0 mg kg^{-1}; chlorpromazine—0·2 and 0·5 mg kg^{-1} (between b and c an additional dose of 3·0 mg kg^{-1} was given); haloperidol—0·2, 0·5, 1·0, and 2·0 mg kg^{-1}. Time lapses: A, between a and b—5 min; B, between a–b and b–c—6 min and 30 min, respectively; C, between a and b—10 min. Haloperidol is the only drug studied that antagonizes the sympatho-inhibitory effect of apomorphine.

the sympathetic activity and prevented the consequences of consecutive apomorphine administration.

Haloperidol in a cumulative dose of 0·4 mg kg^{-1} was effective in antagonizing the action of apomorphine (Fig. 4C). In animals pretreated with apomorphine, inhibition of sympathetic nerve activity elicited by higher doses of EGYT-2509 could not be antagonized by haloperidol.

Discussion

The novel neuroleptic drug EGYT-2509 exerts pharmacological and biochemical effects (Gyüre et al 1985; Petöcz et al 1985; Gacsályi et al 1987) that seem to be partially similar to those of traditional neuroleptics, except for some undesirable side effects (e.g. cataleptogenic, influencing prolactin level).

Since dopaminergic mechanisms are claimed to make a significant contribution to the neuroleptic action (Carlsson 1978; Creese et al 1978; Robertson & MacDonald 1986), we have focused our attention on the interactions of a dopaminergic agonist (apomorphine) and EGYT-2509. As tested on BP and the nictitating membrane reflexes elicited by sciatic nerve stimulation and on spontaneous sympathetic nerve activity, EGYT-2509 has shown, depending on the dose and on the effectors observed, antagonistic as well as agonistic activities with respect to apomorphine.

This kind of dual activity may be supposed even on the grounds of changes of BP in response to EGYT-2509. Its intravenous administration elicits a dose-dependent transient depressor effect (Table 1). This short depressor reaction might be due to some ganglionic blocking activity of EGYT-2509 (Petöcz et al 1985), however, the transient decrease of BP is manifested at lower doses (0·5–1·5 mg kg^{-1}) than the ganglionic blocking effects (2–5 mg kg^{-1}). The hypertension that follows the depressor reaction may be the result of an antidopaminergic activity of EGYT-2509, but its turning into hypotension after a higher dose (18·5 mg kg^{-1}) of EGYT-2509 suggests some dopaminergic agonist activity, too. This suggestion is borne out by the fact that, in cats pretreated with apomorphine, even 8·5 mg kg^{-1} of EGYT-2509 is enough to elicit long-lasting (20–30 min) hypotension.

The testing of the drug on somato-autonomic reflexes has given support for a dose-dependent and target-oriented differentiation of the dopaminergic activity of EGYT-2509. However, to have valid results in this test, some prerequisites are needed. The amplitude and character (pressor or depressor) of BP reactions elicited by somatic nerve stimulation depend on the kind and depth of anaesthesia (Gutman et al 1961; Khayutin 1966; Erdélyi et al 1977). In commonly used types of anaesthesia, nictitating membrane reflexes are not easily evoked (Chen et al 1937; Gellhorn & Redgate 1955; Oono 1965; Molnár et al 1969). Therefore, to test CNS processes integrating somato-autonomic reflexes Molnár et al (1969) proposed the use of superficial urethane anaesthesia, under the condition of which (1) the reflexes of the membrane were not obviously hindered, while its resting tone was stable, (2) BP reflexes were homogeneous: in response to somatic stimuli only pressor reflexes were obtained. Molnár's proposition proved to be an appropriate way in testing the somato-autonomic reflex integration (Dóda et al 1977; Koltai et al 1978; Dóda & György 1982).

Depending on the frequency of stimulation applied, dopaminergic agonists display opposite effects: inhibition and potentiation of BP reflexes (see introduction), i.e. a downward shift in the initial segment of the frequency-response curve and an upward shift in the terminal one. This highly specific change in the frequency-response curve is specifically antagonized by EGYT-2509 (Fig. 2A), proving that in this case the drug is to be classified as a dopaminergic antagonist. This statement is corroborated by the effects seen when EGYT-2509 is given alone: lower doses inhibit BP responses upon stimulation at 2–4 Hz, and high doses are needed to attain inhibition also in the higher range of stimulation frequencies (Table 2A). At the same time, BP reflexes depressed by high doses of EGYT-2509 can be partially restored by haloperidol (Fig. 1)—that substantiates a dopaminergic agonist-like feature, at least in a higher range of dosage.

As for the reactions of the nictitating membrane, they favour the interpretation that EGYT-2509 is a dopaminergic agonist. EGYT-2509 does not influence the apomorphine induced inhibition of nictitating membrane reflexes (Fig. 2B) in the entire range of stimulation frequencies applied. At the same time, the inhibition exerted by EGYT-2509 itself, can be antagonized by haloperidol (Fig. 1).

Dopaminergic agonists, such as apomorphine, piribedil, bromocriptine and pergolide, have been shown to depress spontaneous nerve activity (Jadhav et al 1983; Dóda & György 1984, 1985). The apomorphine-induced diminution of spontaneous nerve activity cannot be antagonized either by EGYT-2509, or by chlorpromazine, moreover, increasing their dose leads to a more intense inhibition of discharges (Fig. 4 A,B). EGYT-2509, given alone, in doses 1 mg kg^{-1} or more displays an inhibitory effect like that due to apomorphine (Fig. 3). In the latter case, however, haloperidol cannot restore spontaneous nerve activity, as it does after apomorphine and the other dopaminergic agonists.

The sympathoinhibitory effect of EGYT-2509 therefore, can hardly be explained by an antidopaminergic action. It cannot be explained by its ganglionic blocking effect (Petöcz et al 1985) either, since the latter is short in duration and ensues only after higher doses than those of EGYT-2509 used in this study to inhibit spontaneous nerve activity.

The diversity of the dopaminergic effects of EGYT-2509, as tested with systemic BP reactions, and reflexes of the nictitating membrane, an organ innervated only by sympathetic efferent fibres (Rosenblueth & Bard 1932; Rothballer & Sharpless 1961; Thompson 1961), and with the changes of spontaneous efferent activity of a single nerve strand, a branch of the renal nerve, may be attributed to differences in the integration of various sympathetic outputs (Weir & MacLennan 1963; Green & Heffron 1966; Dóda et al 1977; Erdélyi et al 1977; Kollai 1983; Molnár et al 1969). The uneven distribution of dopaminergic systems in the CNS seems likely to contribute to the unequal issues of the sympathetic outflow to various targets. In a report (Dóda & György 1982), just in the context with the effects of apomorphine, we have shown that the various somato-autonomic reflexes are organized in different ways.

In the present study, EGYT-2509 proved to be diversely influential on the dopaminergic components of the integration of sympathetic output and somato-autonomic reflexes. It may be that this diversity provides, at least in part, a background for EGYT-2509 to be a non-traditional neuroleptic lacking several undesirable side effects.

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