Pharmacology Biochemistry & Behavior, Vol. 6, pp. 5–10.

Effects of Intrastriatal Injections of Atropine and Methacholine on the Apomorphine-Induced Gnawing in the Rabbit

STANISŁAW WOLFARTH, WACŁAW KOLASIEWICZ

Institute of Pharmacology, Polish Academy of Sciences, 31–344 Kraków, Poland

(Received 24 August 1976)

WOLFARTH, S. AND W. KOLASIEWICZ. *The effects of intrastriatal injections of atropine and methacholine on apomorphine-induced stereotypy in the rabbit.* PHARMAC. BIOCHEM. BEHAV. 6(1) 5–10, 1977. – To find out the anatomical location of the target point of cholinergic-dopaminergic equilibrium, atropine (40 μg) or methacholine (10 μg) were injected through previously implanted cannulas into various places of caudate nucleus and putamen of the rabbit, and the effect of the injections on stereotyped gnawing induced by subcutaneously or intravenously administered apomorphine (1–2 mg/kg) was assessed. The intensity of gnawing was measured using a special apparatus, counting each bite. Atropine inhibited the stereotypy, while metacholine potentiated it. The effects were evident with the method used, but difficult to reveal with the classical method of assessing the intensity of stereotyped behavior, based on visual observation. The results suggest that the striatum is not a target point for the cholinergic component of the cholinergic-dopaminergic equilibrium in the central nervous system.

Apomorphine stereotypy Cholinergic-dopaminergic equilibrium Striatal cholinergic mechanisms
Rabbit

A HYPOFUNCTION of the nigro-neostriatal dopaminergic system is regarded as the main disturbance leading to Parkinson's disease since the report of Ehringer and Hornyiewicz [21] that dopamine level in the striatum and degenerative changes of the cells of substantia nigra appear in the victims of parkinsonism. As both dopaminomimetics and cholinolytics exert a therapeutic effect in the Parkinson's disease, and cholinomimetics exacerbate the symptoms of parkinsonism it is thought that a disturbance in the cholinergic-dopaminergic equilibrium in the extrapyramidal system is the cause of the disease [2, 4, 8, 20, 30, 38, 43]. It has been supposed that the striatum is the pivotal point of the equilibrium, as the levels of both dopamine and acetylcholine, and the activities of enzyme systems for synthesis and catabolism of both the neurotransmitters are the highest in this brain area [2–6, 12, 13, 35, 36, 38, 44, 46], and the electrical stimulation of the afferent fibers to the striatum results in an elevation of the level of dopamine in this area [14,35].

Although the interaction between dopamine and acetylcholine in the central nervous system has been demonstrated in various experimental models, and in various animals including the man [2–4, 6, 9, 13, 26–28, 31, 32, 37, 41], the belief that the striatum is the pivotal point for the cholinergic-dopaminergic balance seems now less acceptible as previously [3, 6, 18, 34, 47–49].

Apomorphine-induced stereotypy in rats or in rabbits represents one of the laboratory models for the evaluation of the activity of the dopaminergic system [7, 18, 26 34, 38, 41, 42, 47–49, 51]. Using this model, the cholinergic-dopaminergic interaction was approached in the present investigation.

It was expected that the intrastriatal injections of a cholinolytic or a cholinomimetic will disturb the cholinergic-dopaminergic equilibrium in the striatum, the treatment with a cholinolytic shifting the balance to the predominance of dopamine system and vice versa. We report here that, contrary to expectations, intrastriatal injection of a cholinolytic depresses, and that of cholinomimetic intensifies the stereotyped gnawing produced by apomorphine.

METHOD

The experiments were carried out on White Danish male rabbits, weighing 2.5–3 kg at the time of surgery. Stainless steel cannulae (diameter 0.4 mm) were implanted stereotaxically, using the atlas of Ridge [39], under neuroleptanalgesia (morphine, 10 mg/kg + chlorpromazine, 25 mg/kg) into the nucleus caudatus anterior (NC ant., A 4.7, L 2.8, H 8.5), nucleus caudatus medianus (NC med., A 3.7, L 2.8, H 8.0), or putamen (Put., A 2.8, L 5.6, H 12.8). The position of cannula tips was verified histologically at the end of experiments (Fig. 1), and the data obtained from animals with incorrect placement of the cannulae were discarded.

The rabbits were allowed at least two weeks to recover after the surgery. The tests were carried out on the animals placed in a cage made of wood and plastic (Metaplex) (50 × 50 × 50 cm), and were observed by a closed TV circuit.

The intensity of stereotypy was measured using an

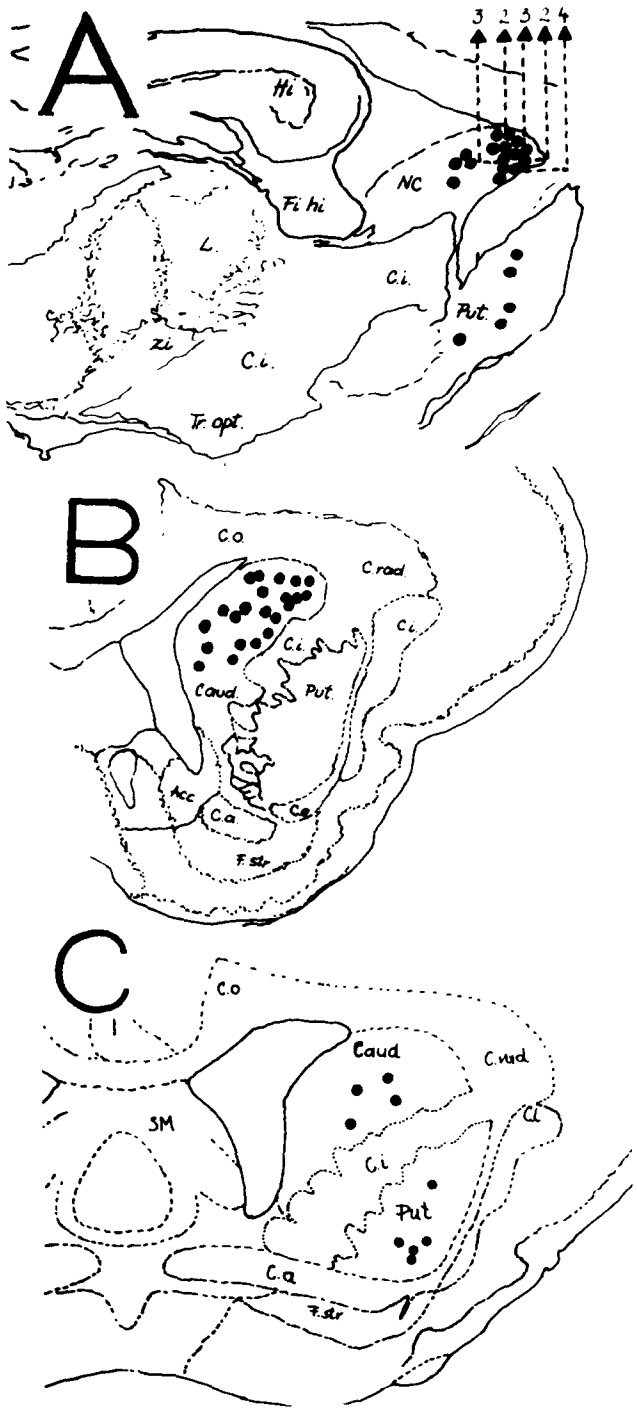

FIG. 1. Diagramatic presentation of the position of cannula tips in the caudatus or putamen of the rabbit brain. Full circles – positions of cannula tips; A – the sagittal section, B – frontal section at 4.7 mm forward from the AP O-line, C – frontal section at 3.2 mm forward from the AP O-line; the number of cannula tips placed in the same positions is marked by arrows. *Abbreviations:* NC – nucl. caudatus, Ci – capsula interna, C rad – corona radiata, Ca – commisura ant., Ce – capsula externa, Hi – hippocampus, Fi hi – fimbria hippocampi, Zi – zona incerta, Acc – nucl. accumbens, SM – nucl. septi med., L – lamina medularis lateralis.

objective method described earlier [33,49]. Briefly, a pair of Teflon R plated with electric contacts was placed in a slot in one corner of the cage. If pressed with the animal's teeth, the plates closed the circuit and activated a counter. If the compulsion of gnawing appeared, the rabbit spontaneously approached and bit the plates, which offered the only possibility for gnawing in the cage. In one experiment the rabbits were restrained and the plates left in the reach of their mouth. Only the animals responding to apomorphine (1 or 2 mg/kg) were used for surgery a week after the positive outcome of the test (not less than 2.7 bites/min measured over a 75 min period). About 10% of the rabbits did not meet the criterion.

Intrastriatal injections were given at a volume of 2 μl through a double-barrel cannula, from a 5 μl Hamilton syringe. The rate of injection was 0.5 μl/min. Atropine (Atropine sulfate, Fluka AG) 40 μg of metacholine (Mecholyl chloride, Merck, Sharp and Dohme) 10 μg, were dissolved in bidistelled water. The water was also used for control injections [50]. The rabbits received apomorphine (Apomorphine sulfate, McFarlane), 1 or 2 mg/kg IV or SC, 30 min after the intrastriatal injection. The experiments were carried out for 75 min after the apomorphine injection. Each rabbit was tested three times only, receiving intrastriatal injection of water, atropine and metacholine in a randomized order. The tests were spaced by intervals of at least 4 days. Statistical significance of the difference after intrastriatal treatment with water and a drug was calculated using the Student's *t*-test for paired comparisons. The local damage to brain tissue was negligible, as only three injections were given through each cannula.

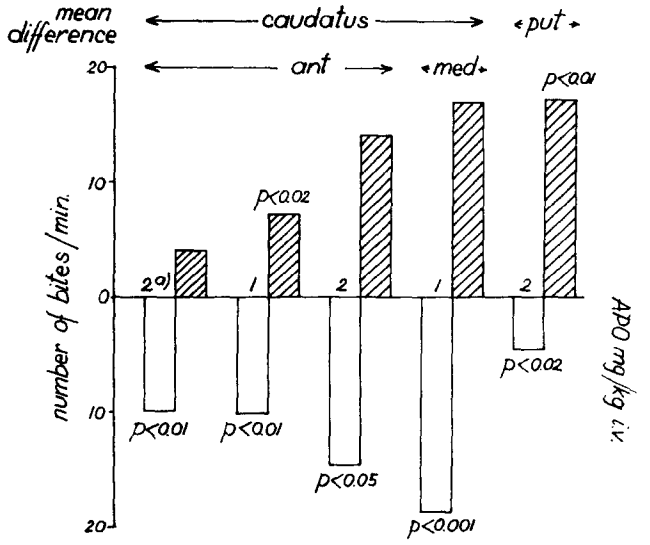

FIG. 2. The effects of intrastriatal injections of atropine and methacholine on apomorphine-induced stereotyped gnawing in the rabbit. 0-line – control (water), open bars – atropine (40 μg), hatched bars – methacholine (10 μg), (a) – apomorphine was injected subcutaneously to immobilized rabbits.

RESULTS

The overall results are presented in Fig. 2. Regardless of location of injection in the striatum (NC ant, NC med, or Put) atropine depressed, while metacholine intensified the gnawing syndrome produced by apomorphine. The action of drugs affecting the cholinergic system seems to depend

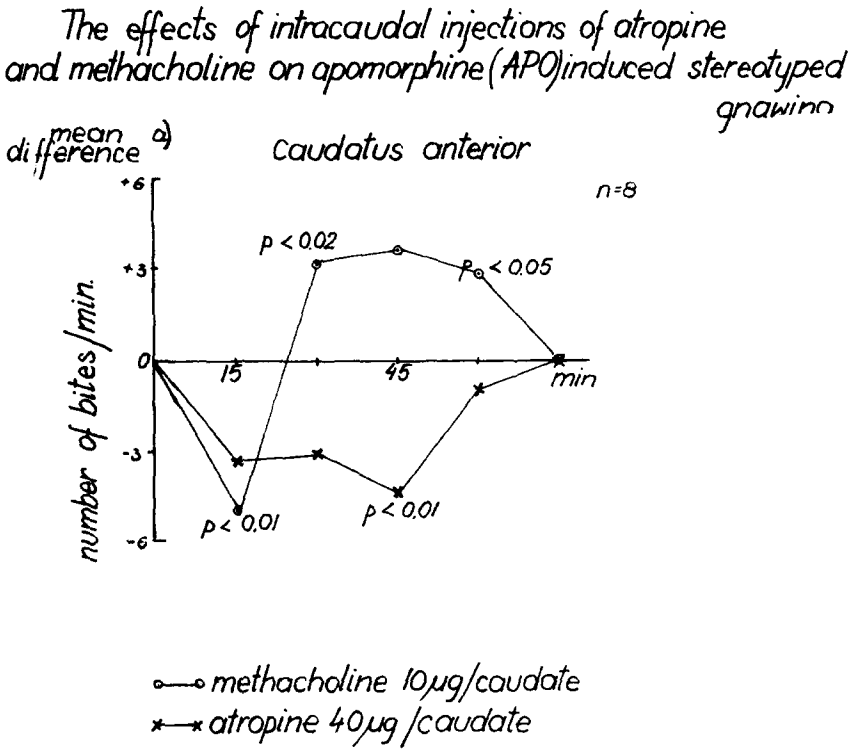

FIG. 3. The effects of intracaudal injections of atropine and methacholine on apomorphine-induced stereotyped gnawing in the rabbit (chronogram). Injections were placed in the nucleus caudatus anterior; 0-line – control (water, x—x atropine (40 μg), o—o methacholine (10 μg); (a) – apomorphine was injected subcutaneously to immobilized rabbits.

upon the availability of apomorphine at the receptor site, as their effects were more pronounced after intravenous than after subcutaneous injections of apomorphine, and were stronger after a higher (2 mg/kg) than after a lower (1 mg/kg) dose. The intensity of gnawing in rabbits pretreated with metacholine was so high (often over 50 bites per min over the period of 75 min) that the rabbits bled from their gums, and even broke the incisors. Following the intravenous injection of apomorphine, the period of stereotyped sniffing and licking was very short, and compulsive biting appeared within a few minutes.

If apomorphine was given subcutaneously to rabbits receiving methacholine intrastriatally, the effect was biphasic for a short period of time the biting was less intensive than in control, water-pretreated rabbits, but than it was intensified for a prolonged period of time (Fig. 3). In contrast, the action of intravenously administered apomorphine was intensified from the very beginning by methacholine pretreatment (Fig. 4). Apomorphine effects were consistently depressed in rabbits pretreated with atropine, regardless of the way of administration of the dopaminergic agent (Figs. 2, 3 and 4).

Although in the experiments with subcutaneous administration of apomorphine the rabbits were immobilized, this did not affect the course of stereotypy, as it had been found in additional experiments, not shown in the figures.

DISCUSSION

Our results now, show that injected into the corpus striatum, atropine antagonizes, and methacholine potentiates the stereotypy induced by apomorphine. The effects do not depend on the location of the injection in the caudate, and are also present if the compounds are injected into the putamen. This suggests the absence of specific macroscopic areas in the striatum, differently responding to drugs affecting cholinergic system. A cholinolytic, atropine, produced an effect opposite to that of a cholinomimetic, methacholine. The results were, however, surprising, as one would rather expect that cholinolytics should potentiate, while cholinomimetics should antagonize the effect of apomorphine. In the rat atropine, given intraperitoneally, potentiates the apomorphine stereotypy and physostigmine abolishes it [26,27]. Moreover, clinical findings indicate that cholinolytics improve the impairment of extrapyramidal functions caused by hypofunction of extrapyramidal dopaminergic system [20, 30, 31, 43].

The Parkinson's disease results from a hypofunction of the central dopamine system, and the therapy of parkinsonism consists either of substitution of the neurotransmitter by administration of a dopamine precursor, dihydroxyphenylalanine (L-DOPA), or by treatment with drugs stimulating dopamine receptors, as amantadine or apomorphine [8, 17, 21, 25, 30, 38, 45], or by therapy with cholinolytics, such as atropine or benzhexal [20, 30, 31]. Neuroleptic drugs, substances which inhibit the flow of impulses through the dopaminergic synapse, precipitate the parkinsonian syndrome [30,45], and both neuroleptics and cholinomimetics intesify the symptoms of Parkinson's disease [20, 30, 31, 45[. The cholinolytic action of some antihistaminic drugs has been employed for the treatment of post-drug parkinsonism, developed in the course of treatment with neuroleptics [30].

The clinical findings, corroborated by a vast number of pharmacological and biochemical studies on animals [2, 9,

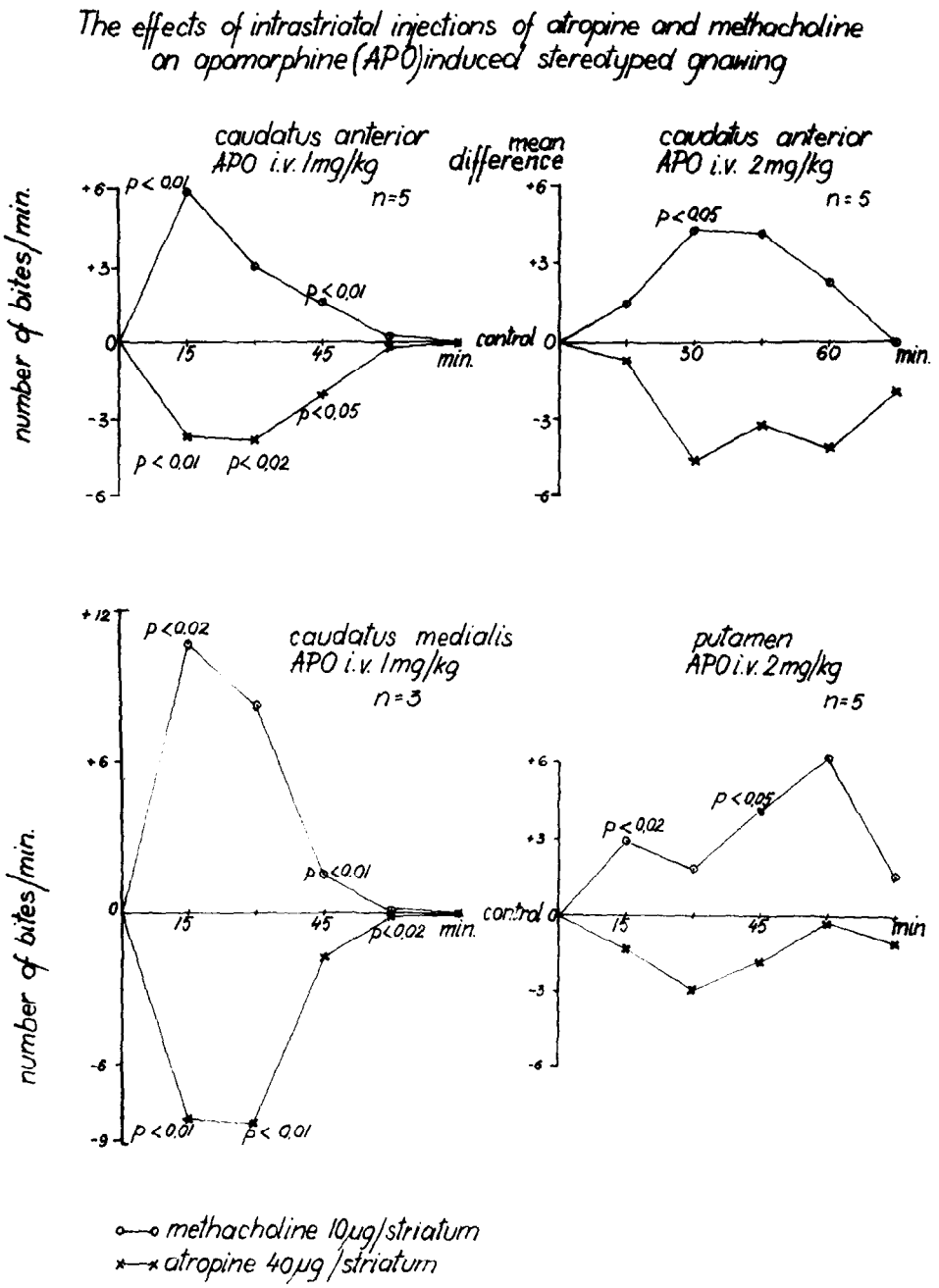

FIG. 4. The effects of intrastriatal injections of atropine and methacholine on apomorphine-induced stereotyped gnawing in the rabbit (chronogram).

10, 27, 32, 37, 41, 43] allowed to put forward a hypothesis, that in the Parkinson's disease the central cholinergic-dopaminergic equilibrium is shifted so, that a relative hyperfunction of cholinergic system develops. These studies prove clearly that the cholinergic and the dopaminergic systems are mutually antagonistic.

The results presented in this paper indicate that the striatum cannot be the only site of the cholinergic component of the dopaminergic-cholinergic equilibrium, as the methacholine-induced stimulation of the cholinergic system in this area produces effects synergistic rather than antagonistic to the stimulation of central dopamine system induced by systemic injections of apomorphine. The fact that atropine, a cholinolytic given intrastriatally inhibits the apomorphine-induced stereotyped gnawing supports this conclusion.

Several early data suggested that the striatum is the pivotal point of cholinergic-dopaminergic equilibrium. It has been found, however, by Divac [18], McKenzie [34], and Wolfarth [47,48] that even almost total bilateral extirpation or lesion of the striatum (caudate and putamen) in the rat does not prevent the development of apomorphine-induced stereotyped gnawing, but even potentiates it. Although apomorphine is known to stimulate the

striatal dopamine receptors [40], these results rule out the striatum as the target point for the apomorphine-induced stereotyped gnawing; they also seem to indicate that the striatum cannot be the only site of the dopaminergic component of the cholinergic-dopaminergic equilibrium. Thus the role of the striatum as the sole target point for both components of the cholinergic-dopaminergic equilibrium seems to be highly improbable.

The problem of the involvement of two kinds of striatal dopamine receptors [15] in the dopaminergic-cholinergic equilibrium may be, however, of importance. Unfortuantely as apomorphine was given peripherally both types of the receptors were simultaneously stimulated and the net effect was observed. To the contrary, the cholinergic system in the striatum seems to be homogenous as the results of intrastriatal injections of drugs affecting the system did not depend on the exact localization of the injection within the striatum.

It is worth noting that intracaudal injection of atropine in the rat [16] produced tremor which was blocked by the administration of tremorine and oxotremorine. This shows that intracaudal injection of atropine may produce an effect usually regarded as a consequence of cholinergic stimulation.

A vast body of evidence indicates that cholinergic receptors are present in the substantia nigra [1, 6, 11, 13, 19, 28, 29, 42, 51]. The intranigral injections of cholinomimetics such as acetylcholine, methacholine, or neostigmine produce stereotypy and epileptoidal discharges, which are prevented by a previous peripheral adminstration of a butyrophenone neuroleptic, spiperone [51]. Conversely, the symptoms of catalepsy appearing after treatment with spiperone, disappear after intranigral injection of neostigmine [51]. It might be speculated, then, that the substantia nigra is the target point for the cholinergic component of the cholinergic-dopaminergic equilibrium in the sense in which this term is used to explain the effects of pharacotherapy of the Parkinson's disease.

The nigral target point for the dopaminergic component of the cholinergic-dopaminergic equilibrium is also suggested by the results of Aghajanian and Bunney [1], who reported that apomorphine iontophoretically applied onto the cells of substantia nigra, inhibits the activity of the neurons of the nigro-neostriatal pathway, while a preceding adminstration of chlorpromazine or haloperidol prevents those effects. It might be suggested that the mutual annihilation of the effects of systemically administered spiperone and intranigrally injected cholinomimetics [51] depends exclusively on the action of those coupounds within the substantia nigra. This may be also indicated by the findings that intranigral injections of atropine results in an elevation of the level of homovanilic acid (HVA) in the corpus striatum [6], while the injection of carbachol into the substantia nigra produces an opposite effect [52].

If the level of HVA may be regarded as a measure of activity of dopaminergic system, these results indicate that a blockade of the cholinergic receptor in the substantia nigra increase the activity of the striatal dopaminergic system, while tha stimulation of the cholinergic nigral receptor depresses the dopamine system in the striatum.

These data, and tha antagonistic action of intranigral injections of apomorphine and carbachol [52] indicate that it is the substantia nigra, which can play an important role in the cholinergic-dopaminergic equilibrium. In this brain area, after all, dopaminergic and cholinergic systems show a clear functional antagonism.

However, our further studies [53] and numerous reports from the literature, [13, 22–25, 28, 35] suggest that the cholinergic-dopaminergic interaction cannot be vested in one brain structure only, but it is rather a resultant of an intricate interplay of inhibitory and stimulatory effects of dopaminergic and cholinergic structures located in various brain areas. It does not seem likely that the drugs useful in the therapy of Parkinson's disease act on single structure only, being it the striatum, substantia nigra, or even some thalamic muclei [7, 23–25, 35] as these drugs are given systemically, they may reach various areas of the brain at different times, they may have different affinities to the receptors in these areas and produce a complex end-result, defined heuristically as a change in the dopaminergic-cholinergic equilibrium. An experimental approach with stereotaxic lesions or application of drugs into various brain areas may possibly elucidate the role of a single brain structure, but the assessment of the physiological role of the area incorporated in the interplay of various interconnected brain structures requires more complex studies.

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