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Tacrine-induced tachyphylaxis in gastric smooth muscles

Research Article

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Abstract: Tacrine is a medication applied in cases of mild to moderate dementia in Alzheimer's disease. By blocking acetylcholinesterase activity the drug increases the concentration of acetylcholine, whose effects influence the functions of different organs and systems of the body. The effect of tacrine on smooth muscle preparations isolated from rat stomach was studied by isometric registration of muscle contractility. Our investigations found a specific significant systematic decrease in the strength of consecutive tacrine-induced contractions of smooth muscle preparations, a phenomenon known as tachyphylaxis. The tacrine-induced tachyphylaxis was significantly inhibited by SQ22536 (inhibitor of adenylate cyclase activity), by blockers of nitric oxide synthase and KT5823 (inhibitor of protein kinase G). The process was not influenced by cyclopiazonic acid (specific blocker of sarco/endoplasmic reticulum Ca^{2+}-ATPase,) and atropine (blocker of M-cholinergic receptors). We hypothesize that the overlapping and different time-development of the two opposing processes: smooth muscle contraction caused by acetylcholinesterase inhibition and tacrine-induced relaxation influenced by synthesis of nitric oxide, results in tachyphylaxis.

Keywords: *Tacrine • Tachyphylaxis • Gastric smooth muscles • Adenylate cyclase • Nitric oxide synthases*

Abbreviations:

AC – adenylate cyclase;
CNS – central nervous system;
GC – guanylyl cyclase;
GI – gastrointestinal tract;
MLCPK – myosin light chain protein kinase;
NOSs – nitric oxide synthases;
PKG – protein kinase;
SM – smooth muscles;
SERCA – sarcoplasmic Ca^{2+} pump.

1. Introduction

Tacrine is a medication applied in cases of mild to moderate dementia in Alzheimer's disease [1]. Its main effect is inhibition of acetylcholinesterase action, the enzyme that catalyses acetylcholine hydrolysis [2]. By blocking the enzyme the drug increases the concentration of acetylcholine in the brain, and this increase is believed to be responsible for the improvement of cognitive functions. Tacrine is administered orally four times per day (as tablets of 10, 20, 30 or 40 mg).

The lack of pronounced selectivity in the distribution of tacrine within the body affects a number of other tissues and organs. Some gastrointestinal (GI) tract functions are markedly influenced in particular, and the effect is manifested as adverse drug reactions, such as a feeling of heaviness in the stomach, nausea, vomiting, indigestion, gastric disorders, diarrhea, gastric pains, *etc.* [3,4]. Some of these adverse drug reactions result from non-anticholinesterase or non-cholinergic mechanisms of action [5] on GI tract smooth muscles (SM). These

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mechanisms can either reduce or enhance the effect caused by the central anticholinesterase action of tacrine.

Our preliminary *in vitro* investigations [6] found a reliable systemic decrease in the strength of consecutive tacrine-induced contractions of SM preparations from rat stomach. This type of drug-induced response is referred to as tachyphylaxis. To the best of our knowledge, no previous data of tachyphylaxis have been reported regarding tacrine action on CNS or other tissues, organs and systems.

Any manifestation of tachyphylaxis following consecutive applications of a pharmacologically active substance is interesting from a physiological point of view, since it is usually associated with desensitisation of the system providing a response to drug action. Knowledge of tachyphylaxis is important for the correct application and success of the treatment, as well as for managing and alleviating the side effects of the drug.

The aim of the present study was to clarify some intracellular mechanisms responsible for the occurrence of tachyphylaxis resulting from the action of the anticholinesterase drug tacrine on smooth muscles.

2. Experimental Procedures

2.1 Experimental animals and SM preparations

Adult male Wistar rats weighing 250–280 g were used. The animals were housed in standard laboratory conditions; they had *ad libitum* access to food and tap water and were kept under a 12 h/12 h light/dark cycle. The experiments were carried out in conformity with the requirements of the European Convention (Helsinki, 1975, article 101, paragraph 5). The rats were decapitated under ether anesthesia. Circular gastric corpus SM preparations (13–15 mm long and 1.0–1.1 mm wide; without mucosa) were immediately dissected. The muscle strips were placed in a 20-ml temperature-controlled tissue bath between a fixed glass holder and an isometric force transducer.

During the preliminary dissection procedures the tissues were constantly moistened with a preparation solution tempered at 37°C.

2.2 Cholinesterase activity in smooth gastric tissues

Smooth muscle strips, either controls or treated with different tacrine concentrations, were homogenized in 10 mM Tris-HCl buffer containing 5 mM EDTA, 1 mM N-maleimide, 1 M NaCl, and 1% Triton X-100 in a ratio tissue weight (mg)/buffer volume (µl) 1:25. Following centrifugation, the supernatant was taken for determination of enzyme activity.

Cholinesterase activity was measured indirectly by quantifying the concentration of yellow-colored 5-thio-2-nitrobenzoic acid (TNB) ion using its molecular absorptivity at 412 nm (e=14 220 M^{-1} cm^{-1}) [7]. This ion was formed in the reaction between the reagent 5,5′-dithiobis-2-nitrobenzoic acid (DTNB) and thiocholine, a product of acetylthiocholine hydrolysis by the cholinesterase [8]. In short, 0.1 ml supernatant was mixed with 0.1 ml acetylthiocholine, then 0.8 ml DTNB was added and the absorption at 412 nm was followed for 3 min. One unit of enzyme (µmol/min) was defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole acetylthiocholine for 1 min at 25°C and pH 7.0. The specific enzyme activity was defined as the measured activity related to 1 mg smooth muscle tissue.

2.3 Registration of smooth muscle mechanical activity

The contractile activity of SM preparations was registered isometrically by a Swema tensodetector (Stockholm, Sweden). The mechanical tension of the SM preparations was achieved by stretching the tension system, its initial value corresponding to a stretching force of 10 mN. The Krebs solution that bathed the smooth muscle preparations was aerated with a mixture of 95% O_2 and 5% CO_2 and had pH 7.4 at 37°C. The tonus level of the preparations observed after a 60-minute period of adaptation at stabilized spontaneous activity was accepted as the initial tonus. The alterations in spontaneous mechanical activity and tonus were registered in relation to the latter by means of a Microtechna amplifier (Prague, Czech Republic) and recorded with a Linseis polygraph (Selb, Germany). During the adaptation period the Krebs solution was changed 4 times. The viability of SM preparations was tested periodically by treatment with 1×10^{-6} mol/l acetylcholine.

The effects of drugs and other active substances on SM preparations were tested by adding aliquots of their concentrated solutions to the tissue bath. The aliquots were between 0.5 and 1% of the total Krebs solution volume.

2.4 Drugs, chemicals, solutions

The following substances were used: tacrine, SQ22536 [9-(tetrahydro-2-furanyl)-9H-purin-6-amine], DMSO (dimethyl sulfoxide), L-NAME (L-N^G-nitroarginine methyl ester), aminoguanidine, metrifonat, cyclopiazonic acid and KT5823, all of them purchased from Sigma (St. Louis, MO); acetylcholine from Dispersa (Baeschlin, Germany), galantamine and atropine from Sopharma (Sofia, Bulgaria). The dry substances were dissolved in the solvent recommended by the producer immediately prior to the experiments.

The Krebs solution contained the following (in mM): NaCl 120; KCl 5.9; $CaCl_2$ 2.5; $MgCl_2$ 1.2; NaH_2PO_4 1.2; $NaHCO_3$ 15.4 and glucose 11.5. The preparation solution contained NaCl/KCl/$CaCl_2$ in a ratio of 27.2/1.1/1. All chemicals used to prepare both solutions were produced by Merck (Darmstadt, Germany). The pH value was measured by a microcomputer pH-meter, model 6201, produced by Jenco Electronics LTD (UK).

2.5 Statistical processing of the results

Values are reported as mean ± standard error of the mean (SEM) with *n* referring to the number of muscle preparations per group. Statistical significance was evaluated using an independent-sample *t*-test (two-tailed) for single point comparisons. Group mean differences were considered significant at $P<0.05$. All statistical analyses were performed using specialized SPSS software, version 8.0 (SPSS Inc. Chicago, IL).

3. Results

3.1 Effects of tacrine on contractile activity

The application of tacrine in the tissue bath in concentrations lower than 1×10^{-5} mol/l (down to 1×10^{-7} mol/l) promoted a contraction of the SM preparations. However, after washing the tissue and treating with tacrine at the same concentration, the recorded contractile effect was significantly reduced. The interval time between two consecutive treatments with tacrine was 40 min. In most experiments the strength of these contractions almost faded away (Figure 1) after a certain number of drug applications, and in some of the preparations the contractile effects were transformed into relaxation ones. The process described developed more rapidly (occurred following fewer applications of the drug) at higher tacrine concentrations (Figure 2)

3.2 Changes in the acetylcholinesterase activity of gastric SM tissues of rat in the presence of tacrine

Measurement of acetylcholinesterase activity following treatment with different tacrine concentrations demonstrated non-linear relationship between the drug concentration and the extent of cholinesterase inhibition (Figure 3). The baseline value of specific enzyme activity measured in SM preparations from gastric corpus in a control group of rats (n=12) was 7.09 U/mg. Incubation with tacrine at concentrations of 1×10^{-6} mol/l and 1×10^{-5} mol/l reduced the specific enzyme activity by 59% and 88% of its baseline value, respectively.

3.3 Metrifonate- and galantamine-induced contractions in repeated consecutive treatments

In experiments analogous to the ones described in 3.1 and carried out with other acetylcholinesterase inhibitors, such as galantamine (1×10^{-5} mol/l) and metrifonate (5×10^{-4} mol/l), the strength of the consecutive drug-induced contractile effects in gastric SM preparations remained reliably unchanged (Table 1).

3.4 Tacrine-induced contractions in consecutive applications of the drug in the presences of a muscarinic antagonist

Following the blockade of M-cholinergic receptors (mAchR) in SM tissue with 1×10^{-6} mol/l atropine, the contractile effects characteristic of the action of 1×10^{-5} mol/l tacrine were not observed. The drug induced SM relaxation, the strength of which increased from the

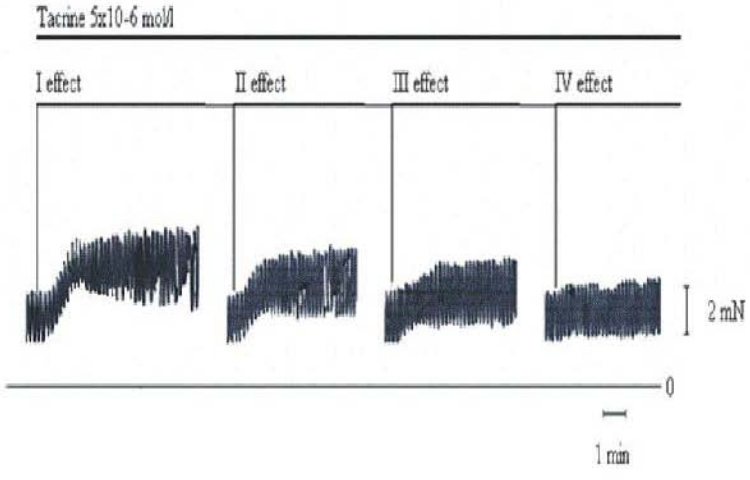

Figure 1. Changes in the strength of tacrine-induced contractile effects in consecutive applications of the drug in equimolar concentration (excerpt from an experimental record).

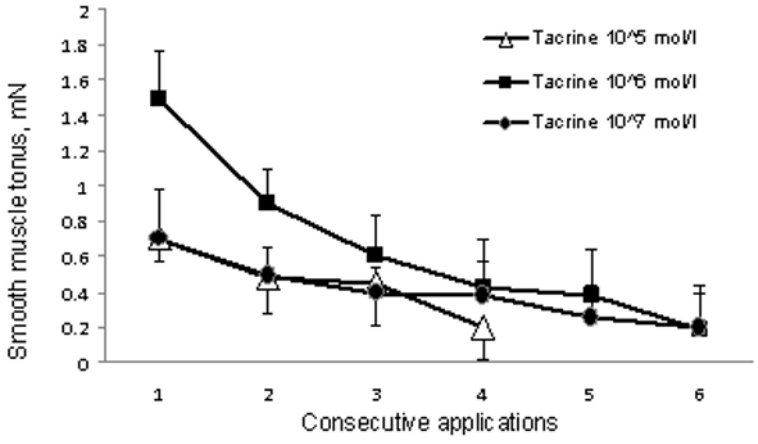

Figure 2. Reduction in the strength of isometrically registered tacrine-induced SM contractions caused by consecutive tacrine treatments (1×10^{-5} mol/l, n=15; 1×10^{-6} mol/l, n=11; 1×10^{-7} mol/l, n=9).

first to the third consecutive application, after which it remained relatively constant. The effects described, parallel with the control contractile reaction to the tacrine treatments, are presented in Figure 4.

3.5. Tacrine-induced contractions in consecutive treatments following inhibition of adenylate cyclase and nitric oxide synthases (NOSs)

In the presence of 5×10^{-7} mol/l SQ22536, a blocker of adenylate cyclase activity, the contractile SM reactions caused by consecutive treatments of gastric SM preparations with 5×10^{-6} mol/l tacrine did not differ reliably one from the other in strength (Figure 5).

In the presence of NOS blockers, such as aminoguanidine (5×10^{-5} mol/l) and L-NAME (1×10^{-5} mol/l), consecutive applications of 1×10^{-5} mol/l tacrine to SM preparations (n=12) under the conditions described above did not reduce progressively the strength of tacrine-induced contractile effects (Figure 6A and 6B).

3.6 Tacrine-induced consecutive SM contractions under conditions of inhibited protein kinase G (PKG) and blocked sarcoplasmic Ca^{2+} pump (SERCA)

KT5823, the inhibitor of PKG, applied at a concentration of 5×10^{-6} mol/l, provoked a mild SM relaxation response. In the presence of KT5823, no reduction was registered in the strength of the contractions of gastric SM preparations (n=6), consecutively induced by 1×10^{-5} mol/l tacrine (Table 2).

The specific SERCA blocker, the cyclopiazonic acid (solvent DMSO), induced a mild SM relaxation

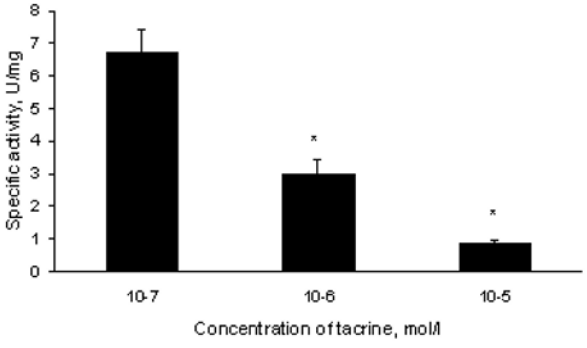

Figure 3. Influence of tacrine on acetylcholinesterase activity of homogenates from SM tissue of rat stomach: 1 – baseline value; 2 – following incubation with 1×10^{-6} mol/l tacrine, 3 – following incubation with 1×10^{-5} mol/l tacrine. * denotes significant differences ($P<0.05$) between the baseline value and values registered in the presence of tacrine.

Number of consecutive treatment	Strength of the Galantamine (1×10^{-5} mol/l)	reaction, mN Metrifonate (5×10^{-4} mol/l)
1	3.7 ± 1.5	1.8 ± 0.8
2	3.2 ± 1.2	1.8 ± 0.7
3	3.5 ± 1.8	1.7 ± 0.6
4	3.0 ± 1.3	1.6 ± 0.4
5	3.0 ± 1.4	1.7 ± 0.9

Table 1. Strength of the reactions of SM preparations from rat stomach registered isometrically in repeated consecutive treatments with 1×10^{-5} mol/l galantamine (n=12) and 5×10^{-4} mol/l metrifonate (n=10).

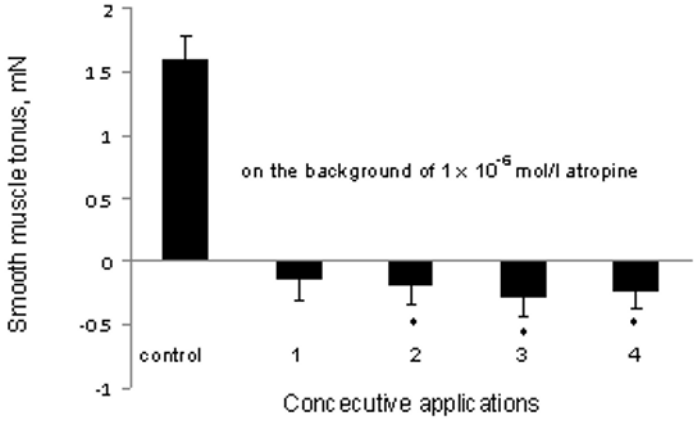

Figure 4. Strength of the reactions of SM preparations from rat stomach (n=9) registered isometrically in repeated consecutive treatments with 1×10^{-5} mol/l tacrine, control ones and in the presence of 1×10^{-6} mol/l atropine (positive values – contractile reaction, negative ones – relaxation reaction). * denotes statistically significant differences ($P<0.05$) between the first and the following three consecutively induced reactions in the presence of 1×10^{-6} mol/l atropine.

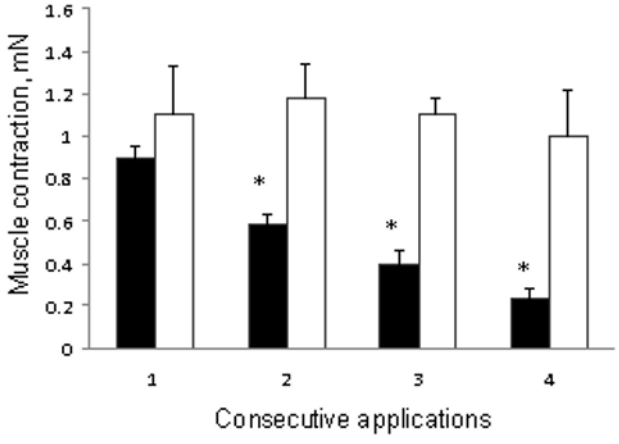

Figure 5. Strength of isometrically registered contractions caused by consecutive treatments with 1×10^{-5} mol/l tacrine in Krebs solution (dark grey columns; n=12) and in the presence of 5×10^{-7} mol/l SQ22536 (white columns; n=12). Statistically significant differences ($P<0.05$) in the strength of both types of contractions, individually for each treatment, are denoted with *.

response. In the presence of 5×10^{-7} mol/l cyclopiazonic acid, the tachyphylactic effect of tacrine (1×10^{-5} mol/l) was preserved in consecutive treatments of gastric SM tissue of rat (n=6) (Table 2).

4. Discussion

The comparison of the reactions of SM preparations, obtained in consecutive treatments with equimolar concentrations of tacrine in the concentration range 1×10^{-7}–1×10^{-5} mol/l, revealed an interesting phenomenon – each treatment that followed, performed in the manner already described, induced a contractile reaction, the

Number of consecutive treatment	Tacrine	KT5823/Tacrine	Cyclopiazonic acid/Tacrine
1	3.3 ± 0.7	3.7 ± 0.9	3.1 ± 0.6
2	1.9 ± 0.3*	3.9 ± 1.5	2.0 ± 0.4
3	1.3 ± 0.4*	3.3 ± 1.4	1.4 ± 0.4*
4	0.9 ± 0.5*	3.5 ± 1.1	1.1 ± 0.6*

Table 2. Changes in the strength of the contractions induced by 4 consecutive treatments with 1×10^{-5} mol/l tacrine in SM preparations in Krebs solution, in the presence of 5×10^{-5} mol/l KT5823 (15 min of incubation) and 5×10^{-7} mol/l cyclopiazonic acid (15 min of incubation), (n=6 for each group). Asterisk denotes statistically significant differences ($P<0.05$) in the strength of contractions compared to the first treatment for each set of experiments.

strength of which was reliably reduced as compared to the one preceding it, which can be considered as a manifestation of tachyphylaxis.

Tacrine inhibits acetylcholinesterase activity and the endogenous acetylcholine accumulated in the tissues causes contractions when acting upon mAchR in SM cells. Following mAchR blockage by atropine, tacrine induced a relaxation effect that was reliably enhanced in repeated consecutive treatments. This peculiarity shows that in the concentration range studied tacrine has another effect, non-cholinesterase in nature, and not associated with mAchR.

A similar conclusion has been drawn from experiments with the cholinesterase inhibitors galantamine and metrifonate [9] – gastric SM tissues contracted in a manner, analogous to the contractions caused by tacrine. The strength of the contractile effects induced by consecutive treatments with galantamine and metrifonate did not decrease reliably. This fact determines the tachyphylaxis registered in tacrine treatments as a phenomenon specific to tacrine and associated with certain non-anticholinesterase mechanisms of its action. The effect did not occur following inhibition of adenylate cyclase (AC) activity by SQ22536 [10], and this determined AC and the increased cAMP level induced by its activation as being immediately involved in the tachyphylactic processes.

Our previous investigations have shown that tacrine exerts some of its non-anticholinesterase effects on gastric SMs by increasing the cAMP level, stimulating adenylate cyclase (AC) and activating the intracellular pathway: cAMP – protein kinase A (PKA) – myosin light chain protein kinase (MLCPK) – the contractile apparatus of SMs [11] The effect of triggering this mechanism occurs as a Ca^{2+}-independent SM relaxation [12] that dominates the behavior of SM preparations at concentrations higher than 1×10^{-5} mol/l.

cAMP and PKA, respectively, are important signal molecules in the body of humans and animals, which are involved in many physiological and pathophysiological processes. The basic mechanism, determining their ability to influence the functions of various intracellular structures, is their immediate (or mediated by other proteins) phosphorylation by PKA [13]. There is evidence that PKA phosphorylates nitric oxide synthases (NOS) [14] and activates them [15], enhancing in this way nitric oxide (NO) synthesis [16].

Reliable inhibition of tacrine-induced tachyphylaxis by NOS blockers (aminoguanidine > L-NAME) [17] supports the assumption that in the concentration range 1×10^{-7}–1×10^{-5} mol/l the drug activates NOS and increases NO levels in SM cells using a similar mechanism. The latter effect very likely brings about

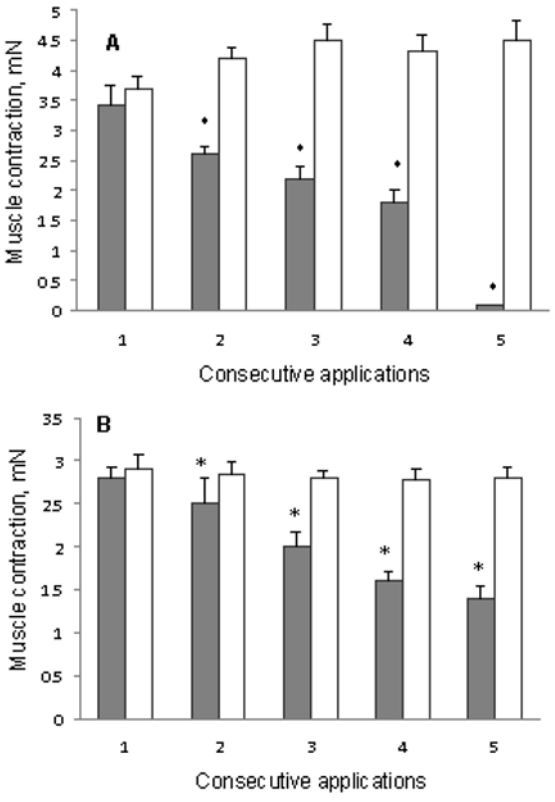

Figure 6. Isometrically registered contractions induced by consecutive treatments with 1×10^{-5} mol/l tacrine in Krebs solution (dark grey columns; n=12) and in the presence of 1×10^{-5} mol/l L-NAME (n=12; A) and aminoguanidine (n=12; B). * denotes statistically significant differences ($P<0.05$) in the strength of each consecutive contraction provoked by tacrine alone and under conditions of inhibited NOS, given individually for each one of the inhibitors.

tacrine-induced relaxation in the presence of atropine. The greater influence of aminoguanidine as compared to L-NAME is an indication of the prevalent involvement of iNOS [18-20], an expression that, in the opinion of some authors [21], is positively influenced by tacrine.

NO activates the soluble guanylyl cyclase (GC), stimulates cGMP synthesis and activates PKG that in its turn activates the myosin light chain phosphatase (MLCP) by phosphorylation [22]. The activation of MLCP induces SM relaxation due to dephosphorylation of the myosin light chain (MLC_{20}) [23]. A convincing proof of the reliability of the above-mentioned facts is the lack of tachyphylaxis after blocking the main cGMP-dependent pathway of NO action upon SM cells by means of PKG inhibition by KT 5823 [24].

A number of studies show presence of a parallel pathway of NO-induced SM relaxation – through non-

cGMP-dependent SERCA stimulation, Ca^{2+} reuptake in SR Ca^{2+}-stores and lowering of the cytosol Ca^{2+} level [25]. This mechanism is considered to act under conditions of preliminary intracellular Ca^{2+} mobilization [26]. In spite of the fact that this state is found in SM contractions provoked by tacrine through endogenous acetylcholine, the lack of effect following SERCA inhibition by its blocker, cyclopiazonic acid [27], refutes any involvement of this pathway in tacrine-induced tachyphylaxis.

The two processes causing opposite reactions, which in our opinion resulted in tachyphylaxis, were a SM contraction caused by endogenous acetylcholine and a relaxation provoked by NO (including PKG stimulation and cGMP formation). The occurrence of these opposing reactions was not simultaneous. Cholinesterase inhibition occurred within a minute, whereas the iNOS expression and NOS activation required a longer period of time and was dependent on the concentration of the activating agent [28]. As a result, the extent of NOS activation was proportional to the number of drug treatments (which required a longer period of time for the tacrine incubation of SM tissues) and occurred more rapidly when higher drug concentrations were applied. Each consecutive tacrine application provided a higher NO level in the SM preparations as compared to the preceding one, as well as a more marked relaxation that reduced to a greater extent the acetylcholine-induced contraction. The superimposition of these two opposing processes, the former gradually increasing in strength, and the latter relatively constant, resulted in the development of the tachyphylaxis that we registered.

Tachyphylaxis occurs in *in vitro* experiments with isolated gastric SMs, in which the increased level of endogenous acetylcholine on the one hand, and cAMP, NO and cGMP on the other, exert contrasting effects. Tachyphylaxis should not be extrapolated to the effects of tacrine on body level, particularly in the CNS, where in many cases the effects of the above-mentioned substances on cell functions associated with the therapeutic application of tacrine are unidirectional.

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