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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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