

tives of a person; but it doesn't mean that a personality is already an organic and harmoniously functioning integrity. Without knowing and without understanding itself, a person doesn't operate itself, rotating in the circle of its mistakes and shortcomings. Difficulties of self-knowledge and self-development result from inaccessibility to knowledge of true "I", that is explained by the existence of two-unity of personal "I" and true "I": the first sometimes doesn't realize the existence of the second and even denies its existence. Actually there are no two "I", as two independent and isolated beings. There is "I", which is shown at different levels of consciousness and self-comprehension. Intuitively feeling itself as a whole and, nevertheless, finding in itself «internal split», a person comes to confusion and can't understand neither itself nor others. "The organic unity" is the purpose of a person, but not its present condition. In especially favorable conditions the finding of «internal unity» is the result of spontaneous growth and maturing, in other cases it is a merited reward received thanks to work on itself, to education or psychocorrection with application of special methods, which facilitate and accelerates the process of self-control, self-development and self-realization, that well influences on the integrative development of individual, mental and professional health.

The researches carried out by us confirm that the organism is trustworthy and is much more capable to self-defense and to self-control, than it is considered to be. Various workings out showed the theoretical need to postulate a certain sort of positive development or tendency to self-actualization of an organism which differs similarly both from aspiration to preservation, maintenance in an equilibrium state and homeostatic process, and from tendency of an organism to react to impulses from the outside world

Thus, it is possible to say that the essence of integrative development of individual, mental and professional health, and also its conservation and strengthening is concluded in self-knowledge, the activity of living position, self-control, self-organizing, self-realization, self-actualization, self-development and self-improvement.

Literature

1. Abulkhanova-Slavsky K.A. Strategy of Life. Moscow: Myusl, 1991. – 299 pages.
2. Rogers K. View of Psychotherapy: transl. from English // Formation of a Person / gen. edition and preface E.I. Isenina. Moscow, 1994. – 480 pages.
3. Perlz F. Workshop on a Geshtalttherapy. Moscow, 2001. – 228 pages.

EFFECTS OF CONCOMITANT EXPOSURE OF DHBE AND A-CTXMII ON NICOTINE-EVOKED [³H]DOPAMINE OVERFLOW IN RAT STRIATAL SLICES

Pivavarchyk M.V.

Yanka Kupala State University,
Grodno, Belarus

Tobacco smoking is the main cause of preventable morbidity in the world. Pharmacotherapy can be useful to achieve long-term abstinence. Pharmacotherapy must provide successful treatment of tobacco dependence and withdrawal, and thereby facilitate efforts to get and prolong tobacco self-control. The most important alkaloid in tobacco, nicotine, activates a few subtypes of nicotinic receptors (nAChRs) which enlarge brain extracellular dopamine (DA) producing nicotine reward leading to addiction. nAChRs are located primarily presynaptically and modulate synaptic activity by regulating dopamine release. Subtype-selective nAChR antagonists that block reward-relevant mesocorticolimbic and nigrostriatal DA release induced by nicotine may offer advantages over existing therapy for smoking cessation. Only a few sybtype-selective antagonists are currently available for use as pharmacological tools to investigate the physiological roles of specific nAChRs. One of them is α -Conotoxin MII (α -CtxMII), which binding remains in brain from $\alpha 3$ knockout mice, but is abolished in $\alpha 6$

knockout mice [1], [2], indicating that α -CtxMII binds to $\alpha 6$ -nAChR subtypes. Other data suggest that $\alpha 6$ -nAChRs may offer a powerful molecular target for a highly selective harmaco-therapeutic strategy to combat nicotine addiction [3].

The purpose of the current study was to determine if $\alpha 4\beta 2$ nicotinic receptor antagonist dihydro- β -erythroidine (DH β E) interacts with α -CtxMII (α -conotoxin MII)-sensitive nAChRs. The maximal concentrations were based on the previously determined I_{max} value for analog and α -CtxMII- induced inhibition of nicotine-evoked [3 H]DA overflow in rat striatal slices. Inhibition of the effect of nicotine by the DH β E alone as well as in combination with α -CtxMII was determined. Rat striatal slices were incubated for 30 min in Krebs' buffer (118 mM NaCl, 4.7 mM KCl, 1.2 mM MgCl₂, 1.0 mM NaH₂PO₄, 1.4 mM CaCl₂, 11.1 mM glucose, 25 mM NaHCO₃, 0.11 mM L-ascorbic acid and 0.004 mM disodiummethylenediamine tetraacetate, pH 7.4, saturated with 95% O₂/5% CO₂) in a metabolic shaker for 30 min. Slices were incubated with 0.1 μ M [3 H]DA for 30 min, transferred to a superfusion chambers maintained at 34°C (Brandel superfusion system 2500) and were superfused for 60 min with oxygenated Krebs' buffer containing both 10 μ M nomifensine (a DA uptake inhibitor) and 10 μ M pargyline (a monoamine oxidase inhibitor), to prevent reuptake and metabolism of [3 H]DA, respectively. Duplicate striatal slices were superfused for 36 min with maximally inhibitory concentrations of α -CtxMII (1 nM) and DH β E (10 μ M). Slices were then superfused with 10 μ M nicotine for an additional 36 min. Separate duplicate slices were also superfused with a maximally inhibitory concentration of mecamylamine (10 μ M) for comparison with a nonselective nAChR antagonist. At the end of the experiment, each slice was solubilized, and the [3 H]-content of the tissue and samples were determined by liquid scintillation spectroscopy.

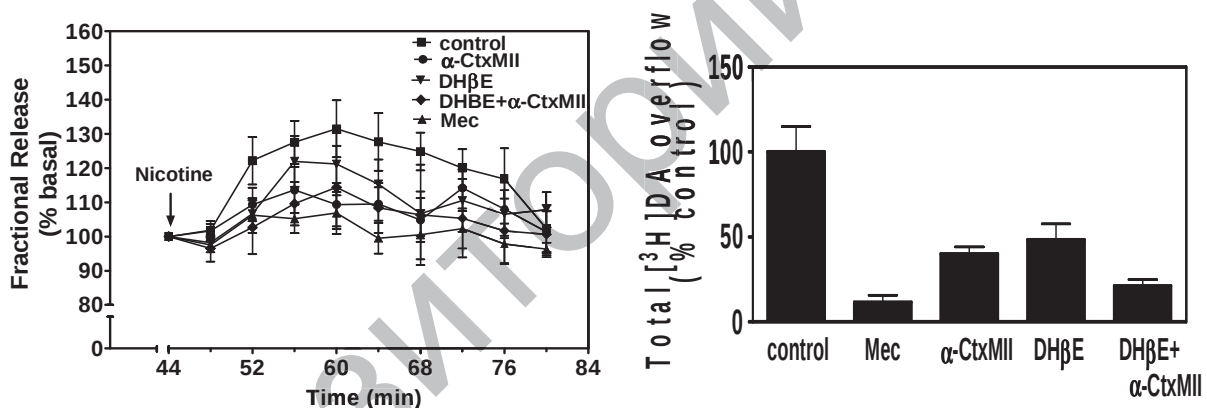


Fig. 1 Concomitant exposure of rat striatal slices to maximally effective concentrations of DH β E and α -CtxMII. Slices were superfused in the absence (control) or presence of 10 μ M mecamylamine (positive control), DH β E, α -CtxMII or α -CtxMII + DH β E for 36 min prior to nicotine addition to the buffer; superfusion continued for 36 min with nicotine added to the buffer. Control represents [3 H]DA overflow in response to 10 μ M nicotine as a percent of tissue [3 H]content, mean $\pm$ S.E.M, n = 5 rats. Left panel: time course of nicotine-evoked [3 H]DA overflow in the absence and presence of DH β E, α -CtxMII or α -CtxMII + DH β E. Data are expressed as fractional release as a percent of basal outflow. Arrow indicates the time point at which nicotine was added to the superfusion buffer.

Current superfusion of rat striatal slices with maximally effective concentrations of DH β E and α -CtxMII resulted in significant inhibition of nicotine-evoked [3 H]DA overflow compared to the within-subject control, i.e. nicotine-evoked [3 H]DA overflow in the absence of the analogs. Importantly, inhibition of nicotine-evoked [3 H]DA overflow resulting from concomitant exposure of DH β E and α -CtxMII was different ($p > 0.05$) from that produced by either antagonist alone. The time course of the response to nicotine and antagonists shows clearly that the inhibition produced by the antagonists presented concomitantly was different

from that following either DH β E or α -CtxMII alone (Fig. 1, left panel). A nonselective nAChR antagonist mecamylamine inhibit 90% of nicotine-evoked [3 H]DA overflow. Thus, the current finding suggests that α 4 β 2 nicotinic receptor antagonist dihydro- β -erythroidine and α -CtxMII inhibit different subtypes of nAChRs. This analogs can be useful as pharmacological tools to investigate the physiological roles of specific α 4 β 2 and α 6-nAChRs.

References

1. Champiaux N, Han ZY, Bessis A, Rossi FM, Zoli M, Marubio L. et al. Distribution and pharmacology of α 6-containing nicotinic acetylcholine receptors analyzed with mutant mice. *J Neurosci.* 2002;22:1208-1217.
 2. Whiteaker P, Peterson CG, Xu W, McIntosh JM, Paylor R, Beaudet AL. et al. Involvement of the alpha3 subunit in central nicotinic binding populations. *J Neurosci.* 2002;22:2522-2529
 3. Exley R, Clements MA, Hartung H, McIntosh MJ, Cragg SJ. α 6 Containing nicotinic acetylcholine receptors dominate the nicotine control of dopamine neurotransmission in nucleus accumbens. *Neuropsychopharmacology.* 2008;33:2158-2166.
- ACKNOWLEDGEMENTS: This research was supported by USPHS Grant U19 DA17548

INHIBITION OF NICOTINE-EVOKED [3 H]DOPAMINE OVERFLOW BY TETRAKIS QUATERNARY AMMONIUM ANALOGS

Pivavarchyk M.V.

Yanka Kupala State University,
Grodno, Belarus

Nicotine, the major psychoactive compound present in tobacco smoke, activates nicotinic acetylcholine receptors (nAChRs), and evokes dopamine (DA) release from presynaptic terminals in the mesolimbic and nigrostriatal dopamine pathways, leading to habitual tobacco use [1], [2]. A novel approach to developing effective tobacco cessation pharmacotherapies is to discover molecules that selectively inhibit acetylcholine receptors subtypes which mediate nicotine-evoked DA release [3].

In order to identify compounds with higher affinity and selectivity as nAChRs antagonists, a series of *tetrakis* quaternary ammonium analogs, containing four quaternary ammonium moieties connected to a central phenylene ring, were used in our experiments. The purpose of the current study was to determine the concentration response of the *tetrakis*-quaternary ammonium compounds (tkPIQB, tkP3HPPB, tkP3BzPB) to inhibit nicotine-evoked [3 H]dopamine release from rat striatal slices.

Rat striatal slices were incubated for 30 min in Krebs' buffer (118 mM NaCl, 4.7 mM KCl, 1.2 mM MgCl₂, 1.0 mM NaH₂PO₄, 1.4 mM CaCl₂, 11.1 mM glucose, 25 mM NaHCO₃, 0.11 mM L-ascorbic acid and 0.004 mM disodiummethylenediamine tetraacetate, pH 7.4, saturated with 95% O₂/5% CO₂) in a metabolic shaker at 34°C for 30 min. Slices were incubated with 0.1 μ M [3 H]DA for 30 min, transferred to a superfusion chambers maintained at 34°C (Brandel superfusion system 2500) and were superfused for 60 min with oxygenated Krebs' buffer containing both 10 μ M nomifensine (a DA uptake inhibitor) and 10 μ M pargyline (a monoamine oxidase inhibitor), to prevent reuptake and metabolism of [3 H]DA, respectively, and to assure that the [3 H] collected in superfusate primarily represented parent neurotransmitter. Slices were superfused for 36 min in the absence (control) or presence of a single concentration of analog. Then, nicotine (10 μ M) was added to the buffer and slices were superfused for an additional 36 min in the absence (control) and presence of analog. At the end of the experiment, each slice was solubilized, and the [3 H]-content of the tissue and samples were determined by liquid scintillation spectroscopy.