EuroSciCon

European Congress on

Pharma

August 13-14, 2018
Paris, France

V E Gmiro et al., Am J Pharmacol Pharmacother 2018, Volume 5
DOI: 10.21767/2393-8862-C1-003

N-DECYLTROPINE (IEM-1556) AS THE FIRST ANALGESIC WITH COMBINED PERIPHERAL VAGUS-STIMULATING AND NICOTINIC CENTRAL BLOCKING EFFECT

V E Gmiro and S E Serdyuk
Institute for Experimental Medicine, St. Petersburg, Russia

The N-decyltropine chloride synthesized by us (IEM-1556), which was previously shown to be an selective blocker of nicotinic cholinergic receptors of parasympathetic ganglia, also revealed the properties of a strong analgesic, which cannot be explained only by its central anticholinergic action in the view of lack of significant analgesic activity in a reference such as central nicotinic receptor antagonist, mecamylamine. Earlier, we obtained data in favor of the participation of adenosine and vagal afferents in the development of the analgesic effect of IEM-1556. The essence of the proposed hypothesis is the ability of IEM-1556 to release endogenous adenosine, stimulating subdiaphragmal vagal afferents as a key link in the mechanism of analgesic action of the drug. In our recent paper, we presented experimental data in favor of this hypothesis. As the reference drug, adenosine was used which had the highest analgesic activity in the tail-flick test in rats associated with stimulation of the vagal afferents of the gastric mucosa. Adenosine in a dose of 22-30 mg/kg and IEM-1556 (N-decyltropin chloride) in a dose of 1-3 mg/kg after intramuscular and intragastric administration cause maximal analgesic effect in the tail-flick test and formalin test in 80-100 % of the rats. Dipyridamole inhibiting reuptake of adenosine, in 9-12 times reduces ED50 of adenosine and IEM-1556, and antagonist of adenosine receptors of 1, 3-dipropyl-8-phenylxanthine (DPX) in 3.8-4.5 times increases ED50 of adenosine and IEM-1556 in both tests. The obtained results evidences in favor of participation of endogenous adenosine in the mechanism of the analgesic action IEM-1556. Preliminary anesthesia of the gastric mucosa with 1% lidocaine and subdiaphragmatic gastric vagotomy almost equally in 3.7-4.4 fold increase ED50 IEM-1556 and adenosine in both tests, indicating the involvement of vagal afferents in the gastric mucosa in the development of analgesic action both IEM-1556, and adenosine. The coincidence of the mechanisms of the vagus-stimulating and analgesic action of exogenous adenosine and IEM-1556 demonstrates that IEM-1556 as a probable liberator of endogenous adenosine after system and oral administration in a low dose of 1-3 mg/kg causes development of analgesia as a result of stimulation of adenosine-sensitive vagal afferents in gastric mucosa. In higher doses the analgesic effect of IEM-1556 (which isn't eliminated by DPX, vagotomy and lidocaine) is presumably explained by additional blockade of cholinergic nicotinic receptors in the CNS. IEM-1556, which includes the central nicotinic blocking and peripheral vagus-stimulating components, is the first exemplar of a new class of double-acting analgesics, potentially effective in the treatment of inflammatory, postoperative and neuropathic pain

1. Remizov I N, Maslov V Y, Purnyn E E, Gmiro V E, Skok V I (1995) Selective pharmacological blockade of synaptic transmission in parasympathetic pathways to the heart in rats. Neurophysiology 27 (5-6), 255—260
2. Tsybenko A, Yanchuk P I, Egorova L S, Gmiro V E (1996) Selective pharmacological blocking of synaptic transmission through the parasympathetic ganglia: effects on the cardiovascular system. *Neurophysiology* 28 (2/3): 119—125.
3. Patent of the Russian Federation No. 2597616, N-alkyl-tropins and N-alkyl-nortropines with n-lytic, antiparkinsonic, antiepileptic, analgesic and antidepressant activity. Published: 09/10/2016, Byul. The patent holder - Gmiro V.E. Co-authors - Shabanov P.D., Serdyuk S.E.
4. Gmiro V E and Serdyuk S E (2016) New innovative drug for the treatment of Parkinson's disease, epilepsy and chronic pain, with a combined n-cholinolitic, adenosine-releasing and vagal-stimulating activity. *The Journal of Pharmaceutics & Drug Delivery Research,* Vol. 5, Issue 4 (Suppl), P. 81.
5. Gmiro V E, Serdyuk S E (2017) Comparative study of analgesic effect of N-decyltropine (IEM-1556), adenosine and mecamylamine. *Russian Journal of Physiology* 103 (10): 1106-1113 (in Russian)

V E Gmiro et al., Am J Pharmacol Pharmacother 2018, Volume 5
DOI: 10.21767/2393-8862-C1-003

Biography

Dr. Valery Gmiro is the leading researcher of Institute Experimental Medicine (Russia). He has published more than 150 papers in reputed journals. The main scientific interest concerns the chemistry and pharmacology of biologically active compounds. He is the USSR State Prise Winner for the investigations in the field of physiology of synaptic transmission. During last years V.Gmiro is working on the problem of the creation of adaptogenic drugs acting through activation of afferent nerves. These drugs were shown to be effective tools to study the mechanisms of transmission of afferent signals and may be of interest in clinic using.

gmiro2119@gmail.com