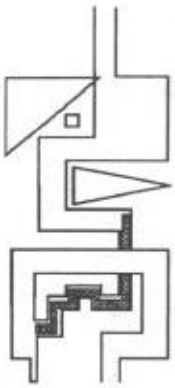

ARCH. GASTROENTEROHEPATOL. 1997; 16 (No.2): 29–32

Effects of fentanyl and its analogs on electric field-stimulated contractions of rat ileum

Delovanje fentanila i njegovih analoga na kontrakcije ileuma pacova izazvane stimulacijom električnim poljem

Slobodan M. JANKOVIĆ, Dušan B. BELESLIN, Milan D. IVANOVIĆ, Dimitrios KOUVELAS, Anastasia ARGYRIOU, Srećko DJORDJEVIĆ and Vassiliku MIRTSOU-FIDANI

Opiates inhibit electrically – stimulated contractions of isolated rat ileum acting on δ – receptors. We have examined effects of fentanyl and its three analogues on contractions of isolated rat ileum stimulated by electric field (20V, 22ms, 1Hz). Fentanyl (from 10^{-9} M to 10^{-7} M) and trans – 3 – (carbomethoxy) fentanyl (from 10^{-7} M to 10^{-5} M) produced concentration – dependent decrease in amplitude of stimulated contractions, only fentanyl was about 40 times more potent. Cis – 3 – (methyl) fentanyl and Cis – 3 – (carbomethoxy) fentanyl did not affect stimulated contractions. Our study suggested that introduction of methyl and carbomethoxy moieties on position 3 of piperidine ring produced loss of fentanyl activity on δ – opioid receptors, cis – orientation being specially unfavourable.

KEY WORDS: fentanyl, analogues, rat, ileum.

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Opijati inhibiraju kontrakcije izolovanog ileuma pacova izazvane stimulacijom električnim poljem, uglavnom delujući preko δ – opioidnih receptora. U našoj studiji smo ispitali dejstva fentanila i njegova tri analoga na kontrakcije izolovanog ileuma pacova izazvane stimulacijom električnim poljem (20V, 22ms, 1Hz). Fentanil (od 10^{-9} M do 10^{-7} M) i trans – 3 – (carbometoksi) fentanil (od 10^{-7} M do 10^{-5} M) su izazvali koncentracija-zavisno smanjenje amplitude stimulisanih kontrakcija, pri čemu je fentanil imao oko 40 puta veću jačinu dejstva. Cis – 3 – (metil) fentanil i Cis – 3 – (carbometoksi) fentanil nisu uticali na stimulisane kontrakcije. Rezultati naše studije sugeriraju da uvođenje metil i karbometoksi radikala na poziciju 3 piperidinskog prstena fentanila dovodi do gubitka njegove aktivnosti na δ – receptorima, posebno ako je u pitanju cis-izomer.

KLJUČNE REČI: fentanil, analog, pacov, ileum

Well known antidiarrhoic action of opioids is the end result of their complex interactions with enteric nervous system (1). It came from numerous experiments on small intestine of different species that prevalent localization of opioid receptors was on presynaptic endings of enteric neurones axons (2). Opioids mostly modulate release of acetylcholine, but other neurotransmitters are affected, too. Different opioid receptor types are involved in different species. In guinea – pig ileum μ and κ receptors are responsible for opioid neuromodulation (3).

Fentanyl binds for and stimulates mostly μ – receptors, but κ and δ – receptors are activated, too (4). The aim of our study was to examine effects of fentanyl and its methyl and carbomethoxy analogues on electric field – stimulated contractions of isolated rat ileum. Minor changes in molecular structure of fentanyl were expected to produce substantial changes in activity on the isolated preparation.

From the Centre for Clinical and Experimental Pharmacology (S.M.J.) and the Department of Urology (S.Dj.), Clinical-Hospital Centre Kragujevac, the Department of Pharmacology, Medical Faculty Belgrade (D.B.B.), the Faculty of Chemistry, Belgrade (M.D.I.), and the Department of Pharmacology, Medical Faculty, Aristotle University of Thessaloniki, Macedonia, Greece (D.K., A.A., V.M-F.)

MATERIALS AND METHODS

Isolated preparations of rat ileum

After fasting 12 hours, 20 white Wistar rats of both sex, weighing between 200 g and 350 g, were killed by cervical dislocation and exsanguinated. The abdomen was opened along the midline. After opening of the abdomen a part of ileum was taken out. This part of ileum was 10 cm far from ileo-cecal connection, it was about 4 cm long and its mesenterium was stripped off. This part of ileum was mounted in isolated organ bath according to the Magnus (5): only one wall of opposite ends of the intestine was tied for the bottom of the bath and the lever, respectively.

The bath and the lever

The strips were mounted in the 15 ml isolated organ bath, filled with Krebs' solution (NaCl 5.54 g, KCl 0.35 g, $MgSO_4$ x $7H_2O$ 0.29 g, $CaCl_2$ 0.28 g, KH_2PO_4 0.16 g, $NaHCO_3$ 2.1 g and