# ACTIVATION OF PERIPHERAL SEROTONIN 5-HT$_{1A}$ AND 5-HT$_{1B/1D}$ RECEPTORS CONTRIBUTES TO THE ANTINOCICEPTIVE PROPERTIES OF METFORMIN

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Several lines of (pre)clinical evidence have emerged that the antidiabetic drug metformin can alleviate inflammatory/neuropathic pain (1). Although the mechanism is not completely understood, there are reports that metformin can affect neurotransmitters involved in pain modulation, such as its ability to increase peripheral serotonin release (2). Here, we evaluated metformin's efficacy following local peripheral administration in an inflammatory pain model and examined the potential involvement of serotonin receptors. We used the formalin test in mice, where we measured duration of nociceptive behavior in the first and second phase of the test. First, we examined the metformin's antinociceptive effects following intraplantar administration. Additionally, the highest tested metformin dose was applied contralateral to the formalin-injected side, to exclude possible systemic effects. In the second part, we evaluated the effects of a 5-HT$_{1A}$ (WAY100635) and 5-HT$_{1B/1D}$ antagonist (GR127935) on the antinociceptive effects of a fixed, effective dose of metformin (antagonists were co-administered intraplantarly with metformin). Metformin (0.1-2 mg/paw) produced significant and dose-dependent antinociceptive effects (32-72%) in the second (inflammatory) phase. Contralateral application of metformin (2 mg/paw) had no significant antinociceptive effects. Both antagonists significantly reduced the antinociceptive effects of metformin (1 mg/paw). The levels of inhibition of metformin's antinociceptive effect produced by WAY100635 were 56% (5 μg/paw) and 82% (7.5 μg/paw), whereas GR127935 inhibited metformin's efficacy by 24% (3.75 μg/paw) and 80% (5 μg/paw). This study demonstrates that peripheral metformin application can produce antinociceptive effects against inflammatory pain and that activation of peripheral 5-HT$_{1A}$ and 5-HT$_{1B/1D}$ receptors contributes to these effects.

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# AKTIVACIJA PERIFERNIH SEROTONINSKIH 5-HT$_{1A}$ I 5-HT$_{1B/1D}$ RECEPTORA DOPRINOSI ANTINOCICEPTIVNOM DEJSTVU METFORMINA

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Postoje brojni dokazi iz (pre)kliničkih studija da metformin, lek iz grupe antidijabetika, može ublažiti inflamatorni/neuropatski bol (1). Iako mehanizam dejstva nije u potpunosti razjašnjen, podaci ukazuju da metformin može uticati na neurotransmitere uključene u modulaciju bola, poput sposobnosti da poveća oslobađanje serotonina na periferiji (2). U ovom radu je ispitana efikasnost metformina nakon lokalne periferne primene u modelu inflamatornog bola, kao i potencijalna uključenost serotoninskih receptora. Korišćen je formalinski test kod miševa, u kome je mereno vreme provedeno u nociceptivnom ponašanju, u prvoj i drugoj fazi testa. Prvo su ispitani antinociceptivni efekti metformina nakon intraplantarne primene. Dodatno, najveća testirana doza metformina je primenjena kontralateralno u odnosu na mesto injektovanja formalina, kako bi se isključili mogući sistemski efekti. U drugom delu studije, ispitani su efekti antagoniste 5-HT$_{1A}$ (WAY100635) i 5-HT$_{1B/1D}$ (GR127935) receptora na antinociceptivno dejstvo fiksne, efektivne doze metformina (antagonisti su primenjeni intraplantarno, istovremeno sa metforminom). Metformin (0,1-2 mg/šapi) je ispoljio značajan i dozno-zavisan antinociceptivni efekat (32-72%) u drugoj (inflamatornoj) fazi testa. Kontralateralna primena metformina (2 mg/šapi) nije imala značajan antinociceptivni efekat. Primenjeni antagonisti su značajno smanjili antinociceptivne efekte metformina (1 mg/šapi). Stepeni inhibicije antinociceptivnog dejstva metformina koje je postigao WAY100635 su bili 56% (5 μg/šapi) i 82% (7,5 μg/šapi), dok je GR127935 inhibirao efikasnost metformina za 24% (3,75 μg/šapi) i 80% (5 μg/šapi). Ova studija je pokazala da periferna primena metformina proizvodi antinociceptivni efekat kod inflamatornog bola i da aktivacija perifernih 5-HT$_{1A}$ i 5-HT$_{1B/1D}$ receptora doprinosi ovom efektu.

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