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The Role of Descending Serotonergic Mechanisms in Anti-hyperalgesic Effect of Zonisamide in a Rat Model for Painful Diabetic Neuropathy

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The aim of this study was to demonstrate the role of descending serotonergic mechanisms in anti-hyperalgesic effectiveness of zonisamide (25 and 50 mg/kg *i.p.*), second generation antiepileptic drug, in a rat model for painful diabetic neuropathy. Diabetic neuropathy was induced by single injection of streptozotocin (STZ) (50 mg/kg; *i.v.*) in male and female Wistar rats (200-250 g) [Oh et al., 2006]. The hot-plate (HP), tail-immersion (TI), and paw pressure withdrawal (PPW) tests were performed to determine thermal and mechanical thresholds 40 min after injection of test drugs (at 22±1ºC, between 10:00 and 18:00 h) [Eddy and Leimback, 1953; Schmauss and Yaksh, 1984; Beyreuther et al., 2006]. The statistical analyses were performed by one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison tests. Differences were considered significant when $P \leq 0.05$. Zonisamide (ZNS) at the doses of 25 and 50 mg/kg [n=10] showed significant anti-hyperalgesic effect as morphine (5 mg/kg) and carbamazepine (32 mg/kg) [n=7], reference drugs, in 3-week diabetic rats [(25 mg/kg ZNS: $P<0.001$ in HP and PPW tests; $P<0.01$ in TI test), (50 mg/kg ZNS: $P<0.001$ in HP, TI and PPW tests), (5 mg/kg morphine: $P<0.001$ in HP,TI and PPW tests), (32 mg/kg carbamazepine: $P<0.001$ in HP and TI tests; $P<0.01$ in PPW test)]. Selective 5-HT_2 antagonist ketanserine (1mg/kg), and selective 5-HT_3 receptor antagonist ondansetron (1mg/kg) [n=10], were used to investigate the role of descending serotonergic pathways in anti-hyperalgesic effects of zonisamide and injected (*i.p.*) 30 min before the doses of ZNS. Each antagonist reversed the effect of zonisamide in the hot-plate and tail-immersion tests significantly [(Ketanserin+25 mg/kg ZNS: $P<0.01$ in HP test; $P<0.05$ in TI test, Ondansetron+25 mg/kg ZNS: $P<0.001$ in HP test; $P<0.05$ in TI test), (Ketanserin+50 mg/kg ZNS and Ondansetron+50 mg/kg ZNS: $P<0.001$ in HP and TI tests)], however relatively in paw pressure withdrawal tests. These results indicate that 5-HT_2 and 5-HT_3 receptors in descending serotonergic pain inhibitory pathways play a role anti-hyperalgesic effect of zonisamide in inhibiting of sensing thermal stimuli, not exactly in mechanical stimuli.

References:

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