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Tramadol effects on the nucleus accumbens – insights from *in vitro* and *in vivo* studies

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Abstract

Background: Tramadol is mainly used for the treatment of moderate to severe pain. It synergistically combines two distinct mechanisms of action, being a selective agonist for μ-opioid receptors (MOR) and inhibiting serotonin and noradrenaline reuptake, which improves its analgesic and safety profile [1]. However, it is not devoid of neurobehavioral toxicity potential [2], whose molecular alterations are not fully clarified. Due to its primary role in reward, motivation and drug self-administration behaviors, the nucleus accumbens (NAC) is anticipated to participate in the mechanisms of tramadol addiction, dependence and toxicity. **Objective:** The aim of this review is to summarize the main neurotoxicity biomarkers and effects of tramadol exposure on the NAC. **Methods:** A bibliographic research of neurotoxicity biomarkers and findings concerning the NAC, upon exposure to tramadol, was performed on the National Library of Medicine (PubMed), with no temporal restrictions and considering *in vitro* and *in vivo* studies. **Results:** *In vivo* studies showed increased levels of MOR, p-CREB and ΔFosB in the NAC after acute and chronic exposure to tramadol (5 and 10 mg/kg) [3]. Even if apoptosis and inflammation are major NAC findings in in vivo studies, autophagy was also upregulated in in vitro studies with PC12 cells exposed to 50 μM tramadol [4]. In addition, it has been found that tramadol enhances dopamine levels in the NAC shell and that NAC cannabinoid receptor 1 (CB1R) is involved in tramadol reinforcing effect and reinstatement [5]. **Conclusions:** In conclusion, although tramadol controls pain more effectively and with fewer adverse events than classical opioids, its neurotoxic potential is of particular concern. The nucleus accumbens has a relevant contribution to such neurobehavioral toxicity, as shown by multiple alterations in important cell death, inflammation and related signaling pathways. A personalized and cautious tramadol prescription is thus mandatory.

Keywords: tramadol; nucleus accumbens; neurobehavioral toxicity; biomarkers

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References

1. Faron-Górecka, A.; Kuśmider, M.; Inan, S. Y.; Siwanowicz, J.; Piwowarczyk, T; Dziedzicka-Wasylewska, M. Long-term exposure of rats to tramadol alters brain dopamine and alpha 1-adrenoceptor function that may be related to antidepressant potency. Eur J Pharmacol (2004), 501(1–3), 103–110.
2. Barbosa, J.; Leal, S.; Pereira, F.C.; Dinis-Oliveira, R.J.; Faria, J. Tramadol and Tapentadol Induce Conditioned Place Preference with a Differential Impact on Rewarding Memory and Incubation of Craving. Pharmaceuticals (2023), 16, 86.

3. Sadat-Shirazi, M.-S.; Babhadi-Ashar, N.; Khalifeh, S.; Mahboubi, S.; Ahmadian-Moghaddam, H.; Zarrindast, M.-R. Tramadol induces changes in Δ-FosB, μ-opioid receptor, and p-CREB level in the nucleus accumbens and prefrontal cortex of male Wistar rat. Am J Drug Alcohol Abuse (2019), 45(1), 84–89.
4. Soltani, R.; Boroujeni, M. E.; Aghajanpour, F.; Khatmi, A.; Ezi, S.; Mirbehbahani, S. H.; Abdollahifar , M.-A.; Akhlaghpasan, M.; Aliaghaei, A.; Heidari, M.-H. Tramadol exposure upregulated apoptosis, inflammation and autophagy in PC12 cells and rat's striatum: An in vitro- in vivo approach. J Chem Neuroanat (2020), 109, 101820.
5. Sadeghi-Adl, M.; Sadat-Shirazi, M.-S; Shahini, F.; Akbarabadi, A.; Khalifeh, S.; Borzabadi, S.; Nasehi, M.; Zarrindast, M.-R. The role of cannabinoid 1 receptor in the nucleus accumbens on tramadol induced conditioning and reinstatement. Life Sci (2020), 260, 118430.