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Impact of tramadol on the hypothalamus: assessment of potential toxicity biomarkers

Nuno J. Henriques [1,2,*], **Ricardo Jorge Dinis-Oliveira** [1,2,3,4], **Joana Barbosa** [1,2,ǂ] **and Juliana Faria** [1,2,ǂ]

[1] Associate Laboratory i4HB - Institute for Health and Bioeconomy, University Institute of Health Sciences - CESPU, 4585-116 Gandra, Portugal
[2] UCIBIO - Applied Molecular Biosciences Unit, Translational Toxicology Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), 4585-116 Gandra, Portugal
[3] Department of Public Health and Forensic Sciences, and Medical Education, Faculty of Medicine, University of Porto, 4200-319 Porto, Portugal
[4] FOREN – Forensic Science Experts, 1400-136 Lisboa, Portugal
[ǂ] these authors contributed equally to this work

* Correspondence: nadjhenriques@outlook.pt

Abstract

Background: Tramadol is a widely prescribed opioid for the control of moderate to severe pain. It is a synthetic opioid, with an atypical mechanism of action, acting as an agonist of μ-opioid receptors and by inhibiting the reuptake of noradrenaline and serotonin [1,2]. In spite of its analgesic effectiveness, tramadol exposure causes several adverse reactions, and despite advancements in understanding its toxicity mechanisms, its neurotoxic effects have not been fully elucidated yet [2,3], particularly its effects on the hypothalamus. **Objective:** The aim of this literature review is to summarize the main biomarkers of hypothalamic neurotoxicity resulting from tramadol exposure. Methods: A bibliographic search carried out in the National Library of Medicine (PubMed) looked at biomarkers of toxicity within the hypothalamic structure resulting from the exposure to tramadol, without temporal restrictions. **Results:** In vivo studies showed that, while tramadol increases the synthesis of prodynorphins at low doses (20 mg/Kg), this effect is not observed at doses of 80 mg/Kg, which results in a decrease in their synthesis in the hypothalamus [2]. After acute tramadol administration, an increase in pERK1/2 levels was observed in the hypothalamus [4]. In vivo tests showed an increase in the expression of IRS2 and glucokinases in the hypothalamus [2]. High reductions in α2-adrenergic receptors in the structure of the hypothalamus have also been reported [5]. **Conclusions:** In summary, while tramadol is effective in pain control, its neurotoxic potential in the hypothalamus is apparent and dependent on the dose administered. It is associated with a decrease in noradrenaline reuptake through downregulation of adrenergic receptors, which can be harmful, as well as an increase in kinase expression or even an increase in the expression of insulin signaling pathway elements. Careful administration of tramadol is imperative due to its neurotoxic potential.

Keywords: tramadol; hypothalamus; neurotoxicity; biomarkers

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References

1. Candeletti, S.; Lopetuso, G.; Cannarsa, R.; Cavina, C.; Romualdi, P. Effects of prolonged treatment with the opiate tramadol on prodynorphin gene expression in rat CNS. J Mol Neurosci (2006), 30(3), 341-7.
2. Choi, S. B.; Jang, J. S.; Park, S. Tramadol enhances hepatic insulin sensitivity via enhancing insulin signaling cascade in the cerebral cortex and hypothalamus of 90% pancreatectomized rats. Brain Res Bull (2005), 67(1-2), 77-86.
3. 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.

4. Omara-Reda, H.; Ouachikh, O.; Durif, F.; Hafidi, A. Acute Tramadol Administration Induces the Expression of pERK1/2 in Different Limbic and Pain Processing Structures. Chronic Pain Manag (2020), 4: 130.
5. Faron-Górecka, A.; Kuśmider, M.; Inan, S. Y.; Siwanowicz, J.; Dziedzicka-Wasylewska, M. Effects of tramadol on α2-adrenergic receptors in the rat brain. Brain Res (2004), 1016(2), 263–267.