The noradrenergic component in tapentadol action counteracts MOR-mediated adverse effects on adult neurogenesis

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Opiates were the first drugs shown to negatively impact neurogenesis in the adult mammalian hippocampus. Literature data also suggest that norepinephrine (NE) is a positive modulator of hippocampal neurogenesis in vitro and in vivo. Based on these observations, we investigated whether tapentadol (TAP), a novel central analgesic combining mu opioid receptor (MOR) agonism with NE reuptake inhibition (NRI), may produce less inhibition of hippocampal neurogenesis compared to morphine. When tested in vitro, morphine inhibited neuronal differentiation, neurite outgrowth and survival of adult mouse hippocampal neural progenitors (NPC) and their progeny, via MOR interaction. In contrast, tapentadol was devoid of these adverse effects on cell survival and only reduced neurite outgrowth and the number of newly generated neurons at concentrations where it is active at the MOR but does not affect NE reuptake. Moreover tapentadol elicited proneurogenic and antiapoptotic effects through activation of α2 and ß2 adrenergic receptors, respectively. Altogether, these data suggest that the noradrenergic component in tapentadol has the potential to counteract the adverse MOR-mediated effects on hippocampal neurogenesis. As a proof of concept, we showed that reboxetine, an NRI antidepressant,counteracted both antineurogenic and proapototic effects of morphine in vitro. In line with these observations, chronic tapentadol treatment did not negatively affect hippocampal neurogenesis *in vivo*. In light of the increasing long-term use of opiates in chronic pain, in principle, tapentadol combined mechanism of action may result in less or no reduction in adult neurogenesis compared to classical opiates. Since the role of neurogenesis in cognition and emotion, the unique features of tapentadol may potentially represent an distinctive advantage also in clinical settings.