Editorial

Preventive Properties of Ramelteon against Cocaine-Induced Autophagia and Apoptosis: A Hypothetic Role of TNF-α Receptor Involvement and JNK/Bcl-2-Beclin1 or Bcl-2/Bax Signaling Pathway

Cocaine is a behavioral stimulant that has greatly increased its use in recent years, according to some reports that the misuse of this drug induces apoptosis and autophagy through the mechanism of neuroinflammatory and oxidative stress, which ultimately leads to neurodegeneration and neural cell death.[1,2] It has also been shown that the activation of inflammatory receptors such as the tumor necrosis factor-alpha (TNF-α) receptor (TNFR) causes the activation of c-Jun N-terminal kinase (JNK) leading to Bcl-2 phosphorylation, which causes the dissociation of Bcl-2 from the Bcl-2/Beclin1 or Bcl-2/Bax complex, causing both apoptosis and autophagia, and thus causing cell death.[3,4] There is evidence that some parts of cocaine-induced neurodegeneration have been mediated by TNFR, but downstream apoptosis and autophagy have not been approved.[5,6] The neuroprotective strategy for the management of cocaine-induced neurodegeneration by modulating the neural-inflammatory signaling pathway and the apoptosis and autophagia processes referred to by a novel neuroprotective agent is continually superior to any other therapeutic approach. It is, therefore, necessary to explain and introduce or develop a new neuroprotective agent. Previous studies have shown that ramelteon, as a melatonin agonist, can act as a neuroprotective agent and inhibit the neuroinflammatory process, but its effects on TNFR and the apoptosis and autophagic signaling pathway have not yet been clarified.[7,8] Therefore, according to the above-mentioned literature, we believed that the use of ramelteon in cocaine-addicted subjects would provide neuroprotection against cocaine-prompted neuro-inflammatory processes and would suggest TNFR-Bcl-2/Beclin1 or TNFR-Bcl-2/Bax signaling pathways and, thus, possibly inhibit cocaine-prompted autophagy and apoptosis, eventually preventing cocaine-prompted cell death [Figure 1]. Nevertheless, further study is needed in order to clarify this suggestion.

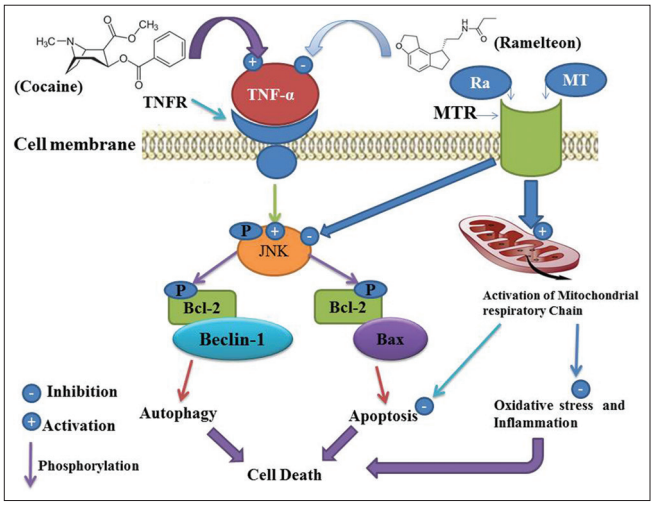

Figure 1: Ramelteon, as a melatonin receptor agonist, can induce inhibition of the effects of cocaine by activating the TNF-α receptor (TNFR)/JNK/Bcl-2-Beclin1 or TNFR/Bcl-2/Bax signaling pathway and cell death caused by it. Melatonin receptor activation by both melatonin and ramelteon also causes mitochondrial biogenesis activation and may cause direct inhibition of JNK/Bcl-2-Beclin1 or JNK/Bcl-2/Bax signaling pathways, which may reduce apoptosis, oxidative stress and inflammation. TNFR: TNF-α receptor, MTR: Melatonin receptor, Ra: Ramelteon, MT: Melatonin

Author's contribution as follow

Conception and design of the hypothesis was done by M.M.

Interpretation of data and review of the literature was done by N.K and F.M.

Drafting the work or revising was done by M.M and S.S.

Designing the figure was done by R.D.

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