Pharmacological characterization of novel halogenated derivatives of JWH-018

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JWH-018 is a synthetic CB_1 and CB_2 agonist illegally marketed as products named 'Spice' or 'herbal blend' for its psychoactive effects which are much higher than those produced by Cannabis. The present study was aimed at investigating the in vitro and in vivo activity of novel halogenated derivatives of JWH-018 (JWH-018-Cl and JWH-018-Br). In vitro competition binding experiments performed on mouse and human CB_1 receptors revealed a high affinity of the novel halogenated compounds. In particular, JWH-018-Cl showed a slightly better affinity than the other examined compounds. The halogenated derivatives were able to bind CB_2 receptors with an affinity similar to that of the reference compound JWH-018. Cyclic AMP experiments performed in CHO cells transfected with human CB_1 receptors revealed a good potency of the examined compounds. The complete inhibition of forskolin-stimulated cAMP production suggests that JWH-018-Cl and JWH-018-Br behave as full agonists showing a maximum effect comparable to JWH-018. In vivo behavioral test in mice were performed to verify the typical responses of cannabinoid agonist on hypothermia, analgesia, hypolocomotion and akinesia. All the tested compounds impaired motor activity and induced catalepsy in mice. Moreover, they increased the mechanical and thermal pain threshold and induced a marked hypothermia. The use of the CB_1 antagonist AM 251 prevented the effect of the tested agonists, suggesting the involvement of CB_1 receptor activation for the observed effects. It is interesting to note that whereas high doses of JWH-018 causes seizures, myoclonia and hyperreflexia, the halogenated compounds were less effective. These data demonstrate that JWH-018-Cl and JWH-018-Br act similarly to JWH-018 while inducing less convulsive episodes and myoclonias. These data support the hypothesis that the halogenated compounds may have been introduced onto market to produce similar intoxicating effects as JWH-018 while causing less side effects.

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