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Effect of synthetic cannabinoids added to smoked herbal mixtures on GABAergic and glutamatergic synaptic transmission in mouse brain slices

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Introduction. The CB_1 cannabinoid receptor is typically located on axon terminals, and its activation leads to presynaptic inhibition of synaptic transmission. The best known agonist of the CB_1 receptor is the phytocannabinoid Δ^9-tetrahydrocannabinol. Recently, synthetic cannabinoids were introduced to the drug market: herbal mixtures for smoking ("Spice", "Lava Red", "Jamaican Gold"…) are "enriched" with such synthetic cannabinoids. Our aim was to characterize the synaptic effects of two frequently abused synthetic aminoalkylindoles, JWH-018 ((1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone) and JWH-210 ((4-ethyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone). The effects of WIN-55212-1 (R(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-yl]-(1-naphthalenyl)methanone) were also studied for comparison.

Methods. 250 µm-thick sagittal slices were prepared from the cerebella of young (8-18 days old) NMRI mice and superfused at room temperature. Purkinje cells in the cerebellar cortex were patch-clamped and spontaneous GABAergic inhibitory postsynaptic currents (sIPSCs) and evoked glutamatergic excitatory postsynaptic currents (eEPSCs) were recorded.

Results. JWH-210 (10^{-6} M) lowered the frequency of sIPSCs (by 28 ± 4 %; $P<0.05$), but did not change their amplitude. JWH-210 (5×10^{-6} M) suppressed the frequency of sIPSCs more strongly (by 52 ± 9 %; $P<0.05$); again, the amplitude was not changed. The CB_1 antagonist taranabant (10^{-6} M) abolished the effect of JWH-210 (10^{-6} M) on the frequency of sIPSCs. Depolarization of the postsynaptic Purkinje cells induced an endocannabinoid- and CB_1 receptor-mediated suppression of the GABAergic inhibitory input to the Purkinje cells (i.e., DSI occurred). DSI was occluded by superfusion of JWH-210 (5×10^{-6} M). JWH-210 (5×10^{-6} M) suppressed the frequency (by 48 ± 12 %; $P<0.05$) but not the amplitude of miniature IPSCs (mIPSCs) recorded in the presence of tetrodotoxin (3×10^{-7} M), pointing to presynaptic inhibition of synaptic transmission. JWH-210 (5×10^{-6} M) decreased the amplitude of glutamatergic eEPSCs (by 67 ± 6 %; $P<0.05$). This was due to presynaptic inhibition, because JWH-210 increased the ratio of the amplitudes of two EPSCs elicited within 40 ms. JWH-018 (10^{-7} and 10^{-6} M) did not affect the GABAergic sIPSCs. JWH-018 (5×10^{-6} M) lowered the frequency of sIPSCs (by 43 ± 8 %; $P<0.05$) without changing their amplitude. WIN-55212-1 (5×10^{-6} M) had a very similar depressive effect on the sIPSCs.

Conclusions. The aminoalkylindoles JWH-210, JWH-018 and WIN-55212-1 inhibit GABAergic synaptic transmission with a presynaptic action. Due to this inhibition they interfere with endocannabinoid-mediated synaptic plasticity. JWH-210 also presynaptically inhibits glutamatergic synaptic transmission. In humans, as additives in herbal mixtures, the synthetic cannabinoids will probably also inhibit GABAergic and glutamatergic synaptic transmission and occlude endocannabinoid-mediated synaptic plasticity. Consequently, impairments of many neuronal functions, including cognitive functions, are to be expected.