Cannabinoid receptor type 1 modulates excitatory and inhibitory neurotransmission in mouse colon.

Abstract:

The effects of cannabinoid receptor agonists and antagonists on smooth muscle resting membrane potentials and on membrane potentials following electrical neuronal stimulation in a myenteric neuron/smooth muscle preparation of wild-type and cannabinoid receptor type 1 (CB1)-deficient mice were investigated in vitro. Double staining for CB1 and nitric oxide synthase (neuronal) was performed to identify the myenteric CB1-expressing neurons. Focal electrical stimulation of the myenteric plexus induced a fast (f) excitatory junction potential (EJP) followed by a fast and a slow (s) inhibitory junction potential (IJP). Treatment of wild-type mice with the endogenous CB1 receptor agonist anandamide reduced EJP while not affecting fIJP and sIJP. EJP was significantly higher in CB1-deficient mice than in wild-type littermate controls, and anandamide induced no effects in CB1-deficient mice. N-arachidonoyl ethanolamide (anandamide), R-[2,3-dihydro-5-methyl 1-3-(4-morpholinylmethyl)pyrrolo[1,2,3,-de]-1,4-benzoxazin-6-yl]-1-naphtalen ylmethanone, a synthetic CB1 receptor agonist, nearly abolished EJP and significantly reduced the fIJP in wild-type mice. N-piperidino-5-(4-chlor ophenyl)-1-(2,4-dichlorophenyl)-4-mety hyl-3-pyrazole-caroxamide (SR141716A), a CB1-specific receptor antagonist, was able to reverse the agonist effects induced in wild-type mice. SR141716A, when given alone, significantly increased EJP in
wild-type mice without affecting IJP in wild-type and EJP in CB1-deficient mice. Interestingly, SR141716A reduced fIJP in CB1-deficient mice. In the mouse colon, nitrergic myenteric neurons do not express CB1, implying that CB1 is expressed in cholinergic neurons, which is in line with the functional data. Finally, excitatory and inhibitory neurotransmission in the mouse colon is modulated by activation of CB1 receptors. The significant increase in EJP in CB1-deficient mice strongly suggests a physiological involvement of CB1 in excitatory cholinergic neurotransmission.