CHARACTERIZATION AND FUNCTIONAL SIGNIFICANCE OF CANNABINOID RECEPTORS IN SKELETAL MUSCLE

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High circulating levels of endocannabinoids have been reported in obese and diabetic individuals. However, the link between activation of the cannabinoid receptors (CB1 and CB2) and impairment in insulin signalling particularly in skeletal muscle is still contradictory (K.A.Lindborg, 2010). The aim of this study was to characterize the cannabinoid receptors (in health and diabetes) and identify their role in cell signalling in human and rat (Wister and Zucker) skm tissues and primary cultured cells using Agilent one colour microarray, Taqman RT-PCR, western blotting and treatment with selective agonists and antagonists. The gene microarray analysis revealed the presence of both CB1 and CB2 as well as the atypical cannabinoid receptors GPR55 and GPR119 in human skm tissue and primary cultured myoblasts and myotubes. RT-PCR analysis confirmed the expression of CB1, CB2 and GPR119 but not GPR55 in both human and rat skm tissues and cells. Interestingly, Wister rat skm tissues had significantly higher level of CB1 (but not CB2) than Zucker obese and lean rats in all types of muscle investigated. In contrast, GPR119 expression was higher in both types of Zucker rats when compared to Wister rats. In cultured human and rat myotubes, treatment with endogenous (AEA) and synthetic (ACEA) CB1 selective agonists increased ERK1/ERK2 and MAPK38 phosphorylation indicating a functional CB1 signalling system. On the other hand, treatment with a CB1 selective antagonist (Rimonabant) attenuated ERK activation in cells obtained from Wister and Zucker lean rats but not Zucker obese rats suggesting that receptors other than CB1 may mediate the ACEA-induced ERK activation in obesity. Moreover, neither ACEA nor Rimonabant affected insulin-stimulated phosphorylation of Akt and GSK3α/β. In conclusion, our data confirm the presence of functional CB1 receptors in both human and rat skm cells and provide evidence for the first time that their intracellular effects are mediated via activation of the ERK signalling pathway but not through the Akt/GSK insulin signalling cascade.