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An Investigation Into The Effects Of Cannabinoids On Neurotrophin Expression In The Rat Brain

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Cannabinoids have been shown to affect cell growth, survival and differentiation. Specifically, the endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) and the phytocannabinoid cannabidiol (CBD) have been shown to influence neuronal growth, differentiation and survival (Gao Y et al, J Neuroscience 30:2017, 2010 and Wolf SA et al, Cell Commun Signal 8:12, 2010). Neuronal cell fate is also influenced by the activity of a family of growth factors known as neurotrophins. Brian-derived neurotrophic factor (BDNF), its receptor neurotrophic tyrosine kinase, receptor, type 2 (TrkB), nerve-growth factor (NGF) and its receptor neurotrophic tyrosine kinase receptor type 1 (TrkA) have been shown to have growth/survival enhancing effects on neurons. To date there has been little investigation into a link between cannabinoid signalling and neurotrophin excpression.

In primary neuronal cultures obtained from 1 day old wistar rats CBD (1µM) was found to induce a time-dependent increase in BDNF mRNA peaking at 2h with a 6-fold increase (6.1±1.0; $p<0.001$, 1-way ANOVA, n=6). NGF, TrkA and TrkB mRNA expression were unaffected by CBD. URB 597 (1µM), a drug which inhibits the hydrolysis of AEA by the enzyme fatty-acid amide hydrolase, induced a similar time-dependent increase in BDNF mRNA expression, peaking at 2h with a 6-fold increase (6.4±1.2; $p<0.001$, 1-way ANOVA, n=6). NGF, TrkA and TrkB mRNA expression were unaffected by URB 597 treatment. URB 602 (100µM), an inhibitor of the enzyme monoacylglycerol lipase which is responsible for 2-AG hydrolysis, induced a 2-fold increase in BDNF mRNA expression after 4h and 8h treatments (2.0±0.3; 2.0±0.1; $p<0.05$, 1-way ANOVA, n=3). A trend towards an increase in NGF mRNA expression following 1, 2, 4, 8 and 24h treatment with URB 602 was observed, however this increase did not reach statistical significance (2.6±0.3; 2.8±0.4; 2.8±0.5; 2.7±0.5; 2.8±0.8; $p=0.06$, 1-way ANOVA, n=3). TrkA and TrkB expression were not altered by URB 602. In order to assess whether cannabinoid signalling plays a role in BDNF expression *in vivo* 3-month old male wistar rats were injected (i.p.) with URB 597 (0.3 mg.kg-1). 3h following injection, serum was prepared from trunk blood and tissue from dentate gyrus and hippocampus was prepared for mRNA and protein analysis. There was a trend towards an increase in BDNF protein expression in the hippocampus (625.4±82.5; 817.2±54.9; $p=0.07$, Student's *t*-test, n=8), however there was no change in BDNF mRNA expression. URB 597 did not affect BDNF expression in dentate gyrus or serum.

These data indicate that cannabinoids increase neurotrophin mRNA expression in primary neuronal cultures. Specifically, 2h CBD treatment enhances BDNF gene expression; this response is replicated with URB 597 suggesting that AEA mirrors the effects of CBD. URB 602 also induces BDNF gene expression which suggests that 2-AG has similar effects to AEA and CBD; however a 4h or 8h treatment is required to induce these effects. 2-AG may also induce expression of NGF at several time-points post treatment. With respect to the AEA induction of BDNF expression these results appear to be replicated in an *in vivo* model. The data suggest that cannabinoid-induced modulation of neuronal function may, at least in part, be due to increased neurotrophin expression.