British Journal of Pharmacology (2003) 140, 439–440

www.nature.com/bjp

COMMENTARY

Neurons on cannabinoids: dead or alive?

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British Journal of Pharmacology (2003) **140,** 439–440. doi:10.1038/sj.bjp.0705465

Keywords: Cannabinoid; neurotoxicity; apoptosis; neuroprotection; c-Jun N-terminal kinase

Abbreviations: JNK, c-Jun N-terminal kinase; THC, Δ^9-tetrahydrocannabinol

Preparations from *Cannabis sativa* (marijuana) have been used for many centuries both medicinally and recreationally. However, the chemical structure of their active components – the cannabinoids – was not elucidated until the early 1960s. Among the $\approx$60 cannabinoids produced by marijuana, Δ^9-tetrahydrocannabinol (THC) is the most relevant one owing to its high potency and abundance (Gaoni & Mechoulam, 1964). Since the early 1990s, it is widely accepted that THC acts in the organism by mimicking endogenous substances – the so-called endocannabinoids (Devane *et al*., 1992) – that bind to and activate specific cell surface cannabinoid receptors, two of which have been cloned and characterized so far from mammalian tissues: CB_1 (Matsuda *et al*., 1990) and CB_2 (Munro *et al*., 1993). These recent findings have led to a remarkable expansion of basic cannabinoid research as well as to a renaissance in the study of the therapeutic value of cannabinoids.

The CB_1 cannabinoid receptor is highly abundant in discrete areas of the brain, and its activation lowers the release of neurotransmitters such as dopamine and GABA, thereby affecting processes such as movement and memory (Piomelli *et al*., 2000). Besides these well-established neuromodulatory events, cannabinoids may control the survival/death decision of neurons (Guzmán *et al*., 2002). Thus, cannabinoids have been shown to protect neurons from toxic insults such as excitotoxicity, traumatic injury and ischaemia both *in vitro* and *in vivo* (Mechoulam *et al*., 2002; van der Stelt *et al*., 2002). This neuroprotective action may rely on different mechanisms, including (i) inhibition of glutamatergic neurotransmission, (ii) antioxidant capacity, (iii) modulation of glial cell function and (iv) control of the microvasculature, and is supported by the observation that the brain overproduces endocannabinoids upon damage (Mechoulam *et al*., 2002; van der Stelt *et al*., 2002). In contrast, a few studies have shown that cannabinoids induce apoptosis of cultured neurons (Chan *et al*., 1998), but the mechanism of this neurotoxic action is largely unknown.

In this issue, Downer *et al*. (2003) show that THC-induced apoptosis of primary rat cortical neurons relies on the activation of the c-Jun N-terminal kinase (JNK) cascade. The JNK protein kinases participate in the blockade of the cell cycle and the induction of cell death triggered by stress signals such as irradiation, heat shock, osmotic shock and pro-inflammatory cytokines. As selective JNK inhibitors are not available, Downer *et al*. (2003) used selective antisense oligonucleotides to target JNK mRNAs and therefore deplete neurons of JNKs. The results of these elegant experiments were rather clear-cut, except perhaps for the relative role of the different JNK isoforms in the apoptotic process.

Cannabinoids may therefore lead to opposite effects on neuron survival/death (Figure 1). It is conceivable that different experimental factors account for this 'ying-yang' action, for example: (i) cannabinoid neuroprotection is usually more evident in whole-animal than in cultured-neuron models, which may result from their aforementioned impact on various brain cell types (neurons, glia, vascular endothelium); (ii) cannabinoids may exert dual effects on neural cell fate depending on signal input (e.g. agonist dose and time of exposure), high inputs usually exerting growth inhibition or death; (iii) endocannabinoids and exogenous cannabinoids may display distinct pharmacological behaviour (e.g. agonistic potency and stability); and (iv) the origin of the neural cell and its stage of differentiation may affect sensitivity to death. Modulation of neural cell fate by cannabinoids is therefore a complex and still obscure issue, and although the bulk of the experimental evidence supports that these compounds protect the brain from damage, the paper by Downer *et al*. (2003) adds a cautionary note to the field.

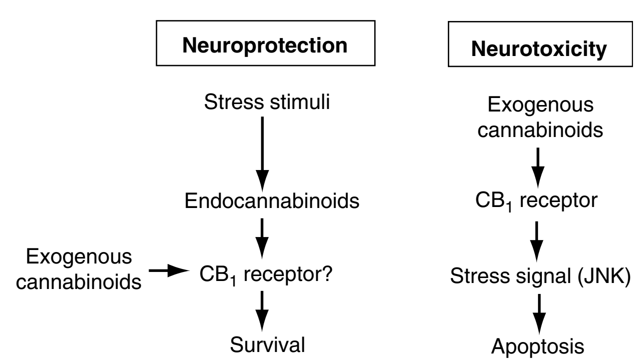

Figure 1 Dual effect of cannabinoids on neuron survival/death. (a) Neuroprotection. Stress stimuli enhance the production of endocannabinoids, which – perhaps *via* CB_1 – would trigger survival signals; exogenous cannabinoids would mimick this action. (b) Neurotoxicity. Cannabinoids *via* CB_1 would activate JNK and this would lead to apoptosis *via* a hitherto unknown mechanism.

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(Received July 16, 2003
Accepted July 21, 2003)