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Letter to the Editor

Cognitive and Neuropsychiatric Consequences of Endocannabinoid Signaling Dysfunction

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Sir

Hill *et al* (2005) report that cognitive deficits induced by chronic stress are associated with a downregulation of hippocampal cannabinoid receptors and reduced levels of 2-AG, an endogenous cannabinoid (eCB). Deficits were reversed by administration of an exogenous cannabinoid. They suggest that a dysfunction of the eCB signaling system may underlie stress-induced cognitive deficits. This important finding provides a missing link with studies of cognitive functioning in human cannabis users. We have previously reported a reversal of electrophysiological indices of selective attention deficits by smoked cannabis in a chronic user (Solowij *et al*, 1995a), who had shown inappropriate processing (deficient filtering) of irrelevant stimuli in the unintoxicated state in accord with our earlier studies of cannabis users (Solowij *et al*, 1991, 1995b; Solowij, 1995, 1998). Similar reversal of this filtering deficit during acute intoxication was also found in a larger sample of chronic users (unpublished data). We had also interpreted the selective attention deficits in chronic users as being due to a dysfunction of the eCB system resulting from chronic exposure to the drug. These processes of selective attention have since been shown to be regulated by excitatory and inhibitory feedback mechanisms via prefrontal cortex (PFC), anterior cingulate and hippocampus (Melara *et al*, 2002). A downregulation of CB1 receptors in hippocampus would disrupt the efficient functioning of the PFC in inhibiting activations to irrelevant stimuli, and similar mechanisms are proposed by Hill *et al* (2005) in relation to processes induced by stress.

The fine-tuning role of the eCB system in regulating cortical information processing is becoming increasingly apparent. Melis *et al* (2004) report a novel eCB-mediated self-regulatory role of dopamine neurons by which they release 2-AG selectively to suppress PFC-stimulation-evoked activity. They also infer that a dysfunction in the eCB system may be involved in altered stress responses and contribute to inappropriate incentive salience to irrelevant stimuli. Cannabinoids potently increase dopamine metabolism and release in PFC but repeat administration leads to a persistent anatomically selective reduction of dopamine metabolism in PFC (Verrico *et al*, 2003), which has now been shown to underlie attentional deficits (Verrico *et al*, 2004). Cannabinoids also have a profound influence on learning and memory via effects on eCB-mediated hippocampal metaplasticity (Mato *et al*, 2004). A dysfunction in hippocampal eCB signaling, and resultant effects on related circuitry, may underlie impairments of learning and memory in chronic cannabis users (Solowij *et al*, 2002).

Hill *et al* (2005) discuss their findings in terms of direct CB ligand/receptor interactions, other neurotransmitters, glucocorticoids, leptin, brain region-specific mechanisms, and other physiological changes that accompany stress. Another putative mechanism may involve fatty acids. We have recently reported on peripheral fatty acid alterations in relation to stress that were differentially evident in schizophrenia patients according to cannabis use history (Monterrubio *et al*, in press). Only former cannabis users with schizophrenia showed a strong positive correlation between stress and linoleic acid levels and inverse correlations between arachidonic acid and fatty acid precursors of lipid signalers that interact with anandamide. Evidence for a dysfunctional eCB system in schizophrenia has been mounting (D'Souza *et al*, 2005; Giuffrida *et al*, 2004) and our findings contribute to evidence linking eCB abnormalities, cannabis use and stress in schizophrenia. Therapeutic modulation of this system for neuropsychiatric and substance use disorders is promising.

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