Correspondence

EDITED BY KHALIDA ISMAIL

Cannabis and psychosis

Arseneault *et al* (2004) very accurately reviewed recent epidemiological data and concluded that cannabis use should now be considered as a component cause leading to psychosis. Yet at least two unanswered questions remain. How can cannabis lead to psychosis? Are some subjects specifically vulnerable to the psychotogenic effect of cannabis?

Several studies, including the Dunedin study, have suggested that adolescents are more vulnerable to cannabis (Arseneault *et al*, 2004). Interestingly, the effects of cannabis on cognitive function also seem more pronounced in adolescents (Ehrenreich *et al*, 1999; Pope *et al*, 2003). This difference might also reflect pre-existing differences in cognitive ability between groups.

Cannabis interferes with endocannabinoid systems, known to be involved in neurodevelopment. In rats, chronic cannabinoid treatment during puberty induces behavioural and cognitive changes that are not found when the treatment is done in adulthood (Schneider & Koch, 2003).

Together, these observations are compatible with the idea that cannabis consumption could alter the last steps of brain maturation, leading to cognitive dysfunction and, in turn, enhancing the risk of psychosis. On the other hand, we recently suggested that genetic variants of the cannabinoid receptor type 1 could be associated with a specific sensitivity to cannabis (Krebs *et al*, 2002). Further studies are now needed to identify subjects 'highly sensitive' to the psychotogenic effect of cannabis, by coupling genetic analysis and cognitive testing to prospective follow-up.

Arseneault, L., Cannon, M., Witton, J., *et al* (2004) Causal association between cannabis and psychosis: examination of the evidence. *British Journal of Psychiatry*, **184**, 110–117.

Ehrenreich, H., Rinn, T., Kunert, H. J., *et al* (1999) Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology*, **142**, 295–301.

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Pope, H. G., Gruber, A. J., Hudson, J. I., *et al* (2003) Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug and Alcohol Dependence*, **69**, 303–310.

Schneider, M. & Koch, M. (2003) Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology*, **28**, 1760–1769.

A. Dervaux, C. Goldberger, X. Laqueille, M.-O. Krebs Service Hospitalo-Universitaire de Santé Mentale et Thérapeutique, Prs H. Lôo et J.-P. Olié, Centre Hospitalier Sainte-Anne, 1 Rue Cabanis, F-75014 Paris, France

The February 2004 issue contained a good review of evidence linking cannabis use to risk for developing schizophrenia (Arseneault *et al*, 2004). Three plausible causal explanations for this association are given. First, that cannabis and/or related drug use is a causal factor for schizophrenia. Second, that the altered mental state induced by cannabis may be mistaken for schizophrenia. Third, that cannabis use may be increased in individuals with the premorbid features of schizophrenia. Arseneault *et al* believe that the evidence favours the first alternative, and we agree. However, we call attention to a fourth possibility. Consider two propositions: (a) features of schizophrenia such as negative symptoms and cognitive impairments precede the onset of psychosis and are considered early morbid rather than premorbid; and (b) schizophrenia is associated with high rates of substance misuse. The cause of substance misuse in schizophrenia is not known. We suggest a fourth hypothesis to explain the cannabis/schizophrenia association. Substance misuse may be a morbid manifestation of some forms of schizophrenia. Vulnerability to substance use may be considered similar to vulnerability to psychosis.

The data review by Arseneault *et al* suggests that the cannabis/schizophrenia association is not based on shared genetic vulnerability. This is of interest to us in that a rodent model of schizophrenia has been developed by one of us (J.I.K.) based on the application of repeated stresses to pregnant rats during the rat equivalent to the second trimester of human pregnancy. The offspring of the stressed dams, once achieving adulthood, manifest the following schizophrenia-like behaviours: diminished cognitive ability on a hippocampal-dependent memory task; impaired gating of event-related potentials and sensory information; augmented behavioural responses to psychostimulants; social apathy and incompetence (Koenig *et al*, 2001; further details available from the authors on request).

In addition, adult rats exposed to stressful gestation consume alcohol in excess compared with control animals. We therefore raise the possibility that aspects of the non-genetic environment may contribute simultaneously to increased risk for cannabis use and increased risk for schizophrenia diathesis.

Declaration of interest

A research contract from Novartis Pharma, AG supported development of the rat model.

Arseneault, L., Cannon, M., Witton, J., *et al* (2004) Causal association between cannabis and psychosis: examination of the evidence. *British Journal of Psychiatry*, **184**, 110–117.

Koenig, J. I., Elmer, G. I., Brady, D., *et al* (2001) In utero experience reprograms the central nervous system: a possible model for schizophrenia. *Schizophrenia Research*, **49** (suppl. 1–2), 92.

J. I. Koenig, W. T. Carpenter University of Maryland School of Medicine, Maryland Psychiatric Research Center, PO Box 21247, Baltimore, MD 21228, USA

I read with great interest the article by Arseneault *et al* (2004). It demonstrates without any doubt that cannabis use in adolescence acts as a causal risk factor for schizophrenia in adulthood. It is, therefore, a pity that the authors had to add the caveat that, since not all adults with schizophrenia used cannabis in adolescence and since the majority of cannabis users do not develop schizophrenia in adulthood, cannabis can be neither a sufficient nor a