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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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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.

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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.

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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

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necessary cause for psychosis. This formulation is erroneous and was used, in exactly the same words, many years ago when prospective studies in the UK established the aetiological role of tobacco in lung cancer. In an elementary textbook on statistics, Schwartz (1999) explains that this error arises from the faulty use of the term 'cause', which applies to the domain of certainty, whereas in the domain of uncertainty (i.e. of illness) the definition of a causal factor is that it provokes an increase in risk, as perfectly demonstrated by the authors. One wonders why they make this elementary error. It is unlikely to be due to psychological resistance, as was the case with tobacco smokers at that time. Perhaps they believe that schizophrenia (or psychosis) is a known disease entity, as defined according to international systems of classification (DSM–IV, ICD–10) which, unfortunately, continue to exclude substance use from their diagnostic criteria.

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.

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Child sexual abuse and substance use disorders: role of psychiatric comorbidity

We read with interest the paper by Spataro *et al* (2004) considering associations between child sexual abuse and subsequent psychopathology using a prospective cohort design. This study clearly indicates a positive association between child sexual abuse and a range of mental disorders, although not substance use disorders. We think that the authors make an important point in their discussion that this latter absence of an association might be at least-partly due to their methodology for assessing psychiatric outcome. They implemented a diagnostic hierarchy in such a way that when substance use problems were accompanied by other psychiatric disorders, these comorbid conditions were counted and not the substance use.

It is important for the reader to know that substantial comorbidity between substance use disorders and other psychiatric disorders is consistently reported (e.g. Kessler *et al*, 1997*a*). Thus, one could suggest that this prospective study does not demonstrate an association between child sexual abuse and more pure forms of substance use disorders. This would be in line with other findings suggesting a lack of association between childhood trauma (including child sexual abuse) and pure substance use disorders, but a strong relationship between childhood trauma and psychiatric comorbidity in substance use disorders (Kessler *et al*, 1997*b*; de Graaf *et al*, 2002).

De Graaf, R., Bijl, R. V., Smit, F., et *al* (2002) Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from The Netherlands Mental Health Survey and Incidence Study. *American Journal of Psychiatry*, **159**, 620–629.

Kessler, R. C., Crum, R. M., Warner, L. A., *et al* (1997*a*) Lifetime co-occurrence of DSM–III–R alcohol abuse and dependence with other psychiatric disorders in the national comorbidity survey. *Archives of General Psychiatry*, **54**, 313–321.

Kessler, R. C., Davis, C. G. & Kendler, K. S. (1997*b*) Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. *Psychological Medicine*, **27**, 1101–1119.

Spataro, J., Mullen, P. E., Burgess, P. M., *et al* (2004) Impact of child sexual abuse on mental health. Prospective study in males and females. *British Journal of Psychiatry*, **184**, 416–421.

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Insulin-like growth factors, insulin resistance and schizophrenia

Abel (Abel, 2004) speculates that imprinting of the gene for insulin-like growth factor-II (IGF-II) as well as other genes may be one pathway through which environmental exposures influence the risk of schizophrenia. We too have hypothesised that factors influencing the growth-hormone–IGF axis may contribute to the well-recognised associations of pre-adult exposures with schizophrenia (Gunnell & Holly, 2004).

We feel that evidence for a direct role of IGF-I is more compelling than that for IGF-II (whose biological functions are poorly understood). Possible pathways for an association with IGF-I lie not only in its role in neurodevelopment but also through its role in neuroprotection following brain damage (e.g. following birth asphyxia, head injury or meningitis) (Gluckman *et al*, 1998). Insulin-like growth factors exert powerful anti-apoptotic actions and low levels may reduce the survival probability of damaged cells. The influence of IGF-I may extend beyond foetal life as low IGF-I is associated with low birth weight, reduced childhood growth and low body mass index, which are, in turn, associated with the development of psychosis (Wahlbeck *et al*, 2001; Gunnell *et al*, 2003). It is therefore possible that low IGF-I levels not only impair neurodevelopment but also render individuals more susceptible to neurodevelopmental insults such as traumatic brain injury and hypoxic brain damage (Gunnell & Holly, 2004).

Several lines of direct and indirect evidence support a possible role of IGF-I in the aetiology of schizophrenia (Gunnell & Holly, 2004). Intriguing indirect evidence for the role of IGF-I, as Abel points out, comes from the observation that low levels protect against a range of different cancers (Renehan *et al*, 2004) and individuals with psychosis, and their families, appear to be at reduced risk of some malignancies. This may well reflect shared genetic influences on IGF levels influencing susceptibility to both schizophrenia and cancer. Evidence for aetiological associations of IGF-II with cancer risk are less consistent than those for IGF-I. A further indirect line of evidence comes from current concern that insulin resistance may both be more common in people with schizophrenia and be precipitated by antipsychotic medication. Prospective studies indicate that low IGF-I levels are associated with the development of insulin resistance (Sandhu *et al*, 2002). We speculate that the co-occurrence of insulin resistance and psychosis may in part arise through the shared susceptibility of both these disorders associated with low IGF-I levels.

Evaluation of the possible role of the IGF-system in schizophrenia might not only further our understanding of the aetiology of this disorder but also give insights into its prevention and the reduction of comorbidities such as insulin resistance.

Abel, K. M. (2004) Foetal origins of schizophrenia: testable hypotheses of genetic and environmental influences. *British Journal of Psychiatry*, **184**, 383–385.

Gluckman, P. D., Guan, J., Williams, C., *et al* (1998) Asphyxial brain injury – the role of the IGF system. *Molecular and Cellular Endocrinology*, **140**, 95–99.

Gunnell, D. & Holly, J. M. P. (2004) Do insulin-like growth factors underlie associations of birth complications, fetal and pre-adult growth with schizophrenia? *Schizophrenia Research*, **67**, 309–311.

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