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Fatty acid relationships in former cannabis users with schizophrenia

Sharon Monterrubio [a,*], Nadia Solowij [a,b], Barbara J. Meyer [c], Nigel Turner [c]

[a] Department of Psychology and Illawarra Institute for Mental Health, University of Wollongong, Northfields Avenue, NSW, 2522, Australia
[b] Neuroscience Institute for Schizophrenia and Allied Disorders (NISAD) Affiliated Scientist, University of Wollongong, NSW, 2522, Australia
[c] Department of Biomedical Science and Metabolic Research Centre, University of Wollongong, NSW, 2522, Australia

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Abstract

Abnormalities in the fatty acid (FA)-based endocannabinoid lipid signaller anandamide, and prevalent cannabis use, have been found to be associated with schizophrenia and may potentially alter stress mechanisms. Other FA-based signallers, however, reportedly enhance anandamide function. The aim of the present study was to investigate the relationship between peripherally-measured levels of the FA sources of anandamide and its related signallers. The authors examined erythrocyte FA levels in patients who were former cannabis users ("C-ever") ($n=6$) or cannabis-naïve ("C-never") ($n=6$), in relation to symptoms of stress measured by the Brief Symptom Inventory (BSI) and the Depression, Anxiety and Stress Scales (DASS). The results showed that, in former cannabis users only, arachidonic acid (AA, anandamide's precursor) was positively correlated with total 16- and 18-carbon monounsaturated and saturated FAs (16,18m+sFAs), precursors of lipid signallers that enhance or interact with anandamide function. In C-ever, both AA and 16,18m+sFAs correlated inversely with stress, while the 18-carbon polyunsaturated FA, linoleic acid, was positively correlated with stress. Although the findings are tentative in this small sample, potential interventions are indicated. Future research may determine whether these FAs are involved in hypothesised links between anandamide abnormalities, cannabis use and stress in schizophrenia.

Keywords: Anandamide; Cannabis; Clozapine; Fatty acids; Schizophrenia; Stress

1. Introduction

Schizophrenia is a complex debilitating disorder in which multiple neural signalling abnormalities are implicated, including abnormalities in the endogenous cannabinoid system. A recent study found that levels of the cannabinoid anandamide in cerebrospinal fluid (CSF) were higher in patients with acute schizophrenia than in healthy individuals, and were inversely associated with symptoms (Giuffrida et al., 2004). A similar relationship between schizophrenia symptoms and AA, the fatty acid (FA) from which anandamide is formed, has also been found in a recent FA supplementation trial: increases in erythrocyte AA correlated positively with reductions in symptoms (Horrobin, 2003b). It has been suggested that interaction between abnormalities in AA metabolism and the anandamide system may contribute to schizophrenia pathology (Horrobin, 2003c). Importantly, inadequate dietary AA can reduce anandamide availability (Berger et al., 2001).

The inverse relationship between anandamide in CSF and symptoms is consistent with animal studies showing that anandamide and related lipid signallers have regulatory and potentially beneficial effects on cell protection and behaviour (Schmid and Berdyshev, 2002). De Marchi et al. (2003) also found elevated anandamide in peripheral blood of patients with acute schizophrenia, and these levels were normalised with clinical remission. The circulating anandamide levels did not correlate with symptom scores (De Marchi et al., 2003), unlike anandamide in CSF (Giuffrida et al., 2004), a difference that may have stemmed from methodological considerations (Giuffrida et al., 2004). It has also been shown that anandamide administration to animals activates stress hormones (Zenor et al., 1999).

Abbreviations: 16,18m+sFAs, total 16- and 18-carbon monounsaturated and saturated fatty acids; 16,18m+sNAEs, *N*-acylethanolamines formed from 16- and 18-carbon fatty acids; AA, arachidonic acid; BSI, Brief Symptom Inventory; CB1, cannabinoid-1; DASS, Depression, Anxiety and Stress Scales; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; LA, linoleic acid; NAE, *N*-acylethanolamine; PUFA, polyunsaturated fatty acid; THC, delta(9)-tetrahydrocannabinol.

* Corresponding author. Tel: +61 2 4221 3742; fax: +61 2 4221 4163.
E-mail address: srm63@uow.edu.au (S. Monterrubio).

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This might indicate that anandamide acts as a stressor, but, equally, could be interpreted as anandamide having a role in the coping mechanism (Zenor et al., 1999), a possibility that may also apply to the study by De Marchi et al. (2003). As well as altered anandamide levels (De Marchi et al., 2003; Giuffrida et al., 2004; Leweke et al., 1999) in schizophrenia, other dysfunctions in the endogenous cannabinoid system include a higher density of cannabinoid (CB1) receptors in postmortem brains from people with schizophrenia (Dean et al., 2001; Zavitsanou et al., 2004).

Since anandamide is involved in stress regulation (Zenor et al., 1999) and cell protection, it is pertinent that a common characteristic of schizophrenia is elevated stress, whether defined as cellular oxidative stress (Mahadik et al., 2001), hormonal activation (Walker and Diforio, 1997), or emotional or psychological response to stressful experiences (Myin-Germeys et al., 2001). Thus, the precise role of anandamide has implications for schizophrenia.

1.1. Cannabis use

Cannabis use is highly prevalent among people with schizophrenia (Kavanagh et al., 2004). Reasons for such extensive use in this population are not well understood. While cannabis may to some extent alleviate negative symptoms, it also increases positive symptoms (Bühler et al., 2002). Interactions between ingestion of exogenous cannabinoids and the endogenous cannabinoid dysfunction in schizophrenia remain underinvestigated.

Substance use has long been associated with induced stress in animals, and with environmental stressors in humans (Piazza and Le Moal, 1998). Spencer et al. (2002) found that the primary motivation for substance use among a cohort of individuals with psychotic disorders was as a means of "coping with unpleasant affect" (p. 233). In a single photon emission computerised tomographic (SPECT) study of an individual with schizophrenia, the smoking of cannabis, reportedly to counter the stress of the procedure, resulted in an immediate calming effect accompanied by a 20% reduction in binding at striatal D2-dopamine receptors (Voruganti et al., 2001). This calming effect, however, was followed by a worsening of psychotic symptoms a few hours later.

1.2. Fatty acids

In schizophrenia, FA levels are studied in erythrocyte membranes, since these show correlation with neuronal phospholipid breakdown and synthesis (Richardson et al., 2001; Yao, 2003). The important neuronal membrane polyunsaturated FAs (PUFAs) that are often abnormally low in erythrocyte membranes of schizophrenia patients are AA, of the omega-6 family, and docosahexaenoic acid (DHA), of the omega-3 family (Horrobin, 2003b). Supplementation with DHA or its precursor, eicosapentaenoic acid (EPA) can increase these FAs and improve symptoms (Horrobin, 2003b). A recent dose-ranging study unexpectedly found that EPA supplementation of 2 mg/day increased erythrocyte AA, an increase that was highly correlated ($r = 0.81$) with symptom reduction (Horrobin, 2003b). It was counter-intuitive that an omega-3 FA (EPA) should lead to an increase in an omega-6 FA (AA), since the two families are competitive. The unexpected finding suggests that the omega-6 and omega-3 families are interdependent (Horrobin, 2003b). Similarly, dietary intake of these FAs or their precursors, particularly the balance between omega-6 and omega-3 families, can affect brain PUFA levels (Barcelo-Coblijn et al., 2003) and can influence or be influenced by both psychological stress (De Gomez Dumm et al., 1978; Maes et al., 2000) and cellular oxidative stress (Saraswathi et al., 2004).

1.3. Anandamide

Anandamide is formed from 20-carbon FA, AA, and belongs to a group of lipid signallers known as *N*-acylethanolamines (NAEs). Release of anandamide is triggered by a rise in intracellular calcium (Hansen et al., 1998), although in rat cortical neurons its release requires the simultaneous activation of specific neurotransmitter receptors (Stella and Piomelli, 2001). While anandamide constitutes less than 1% of NAEs in the mammalian brain, the major constituent brain NAEs are those formed from monounsaturated and saturated FAs of 16-

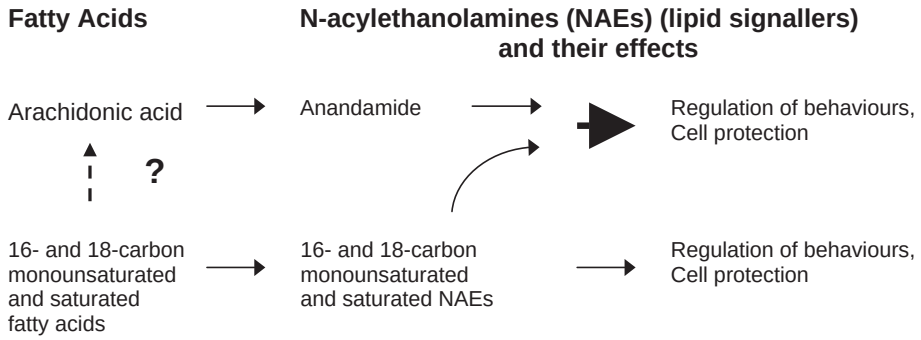

Fig. 1. *N*-acylethanolamines (NAEs) formed from 16- and 18-carbon monounsaturated and saturated fatty acids have been found to interact synergistically with anandamide, an NAE formed from arachidonic acid (AA). The possibility that the fatty acids of 16- and 18-carbons also interact with AA is represented schematically.