Cannabis has been shown to reduce the elevation in anandamide levels in CSF, when compared with patients who had never or only occasionally used cannabis. Additionally, in patients with schizophrenia, cannabis use was associated with lower levels of CSF anandamide and higher levels of 2-AG in serum were observed in frequent compared with infrequent cannabis users. Levels of CSF anandamide were negatively correlated with persisting psychotic symptoms when drug-free. Higher levels of anandamide are associated with a lower risk of psychotic symptoms following cannabis use.

Declaration of interest

None.

Method

The whole sample comprised 15 males and 18 females. One-way analysis of variance (ANOVA) showed no significant group differences in age (22.1 years, s.d. = 2.45) or years of education (16.3 years, s.d. = 1.99). There were no significant group differences in the number of regular alcohol users or level of alcohol use. Urine tests revealed the presence of THC in urine of all heavy cannabis users (n = 10/10), all but one light cannabis users (n = 9/10) and no controls (n = 0/13). One heavy cannabis user and one light cannabis user tested positive for MDMA (3,4-methylenedioxyamphetamine).

The number of regular cannabis users and the number of years of cannabis use was not significantly different between the light and the heavy drug users. The mean age of the whole sample was 22.2 years (s.d. = 2.3) and the majority were female (80%). The whole sample comprised 15 males and 18 females. One-way analysis of variance (ANOVA) showed no significant group differences in age (22.1 years, s.d. = 2.45) or years of education (16.3 years, s.d. = 1.99). There were no significant group differences in the number of regular alcohol users or level of alcohol use. Urine tests revealed the presence of THC in urine of all heavy cannabis users (n = 10/10), all but one light cannabis users (n = 9/10) and no controls (n = 0/13). One heavy cannabis user and one light cannabis user tested positive for MDMA (3,4-methylenedioxyamphetamine).

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(4.65 years, s.d. = 3.28) and heavy (6.5 years, s.d. = 2.92) groups. As expected, heavy users used cannabis on significantly more days per month (22.6 days, s.d. = 7.24) than light users (3.85 days, s.d. = 3.12) ($F(1,16) = 43.02$, $P < 0.001$).

A Kruskal–Wallis test results showed a trend-level group difference for anandamide levels in CSF ($\chi^2 = 4.62$, $P = 0.096$) (Fig. 1). Orthogonal contrasts showed that heavy users had significantly lower CSF anandamide than light users (Mann–Whitney $U$-test = 18.5, $P = 0.015$). There were no significant group differences for OEA, PEA or 2-AG in the CSF. A Kruskal–Wallis test showed a significant group difference ($\chi^2 = 13.669$, $P = 0.001$) in serum 2-AG levels (online Fig. DS1). A subsequent $U$-test indicated that heavy users had significantly higher serum 2-AG levels than controls ($U = 3.000$, $P < 0.001$). There were no significant group differences for OEA, PEA or anandamide in serum. Cerebrospinal fluid anandamide and 2-AG did not correlate with serum. Among cannabis users, CSF anandamide correlated negatively with state psychotic symptoms when non-intoxicated ($r = -0.568$, $P = 0.017$).

Serum levels of 2-AG were found to differ between heavy cannabis users and controls, with greater levels seen in cannabis users. This was an unexpected finding and, given the absence of correlation between serum and CSF levels, one that is difficult to interpret. Indeed, 2-AG is thought to be neuroprotective against excessive glutamate release and previous work has suggested a link between serum 2-AG and depression. However, the link between peripheral endocannabinoids and the CNS remains conjectural at present and warrants further research.

Our findings suggest that anandamide signalling is altered following cannabis use differentially in light and heavy users and psychotic-like symptoms are related to levels of this endocannabinoid in the brain. These findings suggest that healthy individuals who smoke cannabis and have lower levels of anandamide – either endogenously or through their cannabis use – may be more vulnerable to the acute and chronic psychotomimetic effects of cannabis, and therefore potentially more vulnerable to psychosis.

This was the first study to examine CSF eicosanoid levels in cannabis users. The study found lower CSF anandamide in heavy cannabis users compared with light cannabis users. Serum 2-AG levels were significantly higher in cannabis users than in controls. Cerebrospinal fluid anandamide correlated negatively with drug-free psychotic symptoms.

Preclinical work has suggested a downregulation of the endocannabinoid system following chronic THC administration in rats, which is partially supported by these findings. However, the current study extends this to suggest a possible upregulation of endocannabinoid signalling following moderate cannabis use, evident here in the elevated levels of CSF anandamide in light cannabis users but downregulation following heavy use. Control group anandamide levels were intermediate between the two groups, supporting this assertion.

We also observed a negative relationship between CSF anandamide levels and persistent psychotic symptoms. This is consistent with the findings of previous studies and is suggestive of a protective role of anandamide against psychotic-like symptoms, in particular negative symptoms. This may relate to the putative role of anandamide in stabilising dopamine release, given suggestions of increased dopamine release following smoking cannabis. Individuals with lower anandamide may be less able to modulate dopamine release, which increases psychotic-like symptoms both acutely and chronically.

**Discussion**

This was the first study to examine CSF eicosanoid levels in cannabis users. The study found lower CSF anandamide in heavy cannabis users compared with light cannabis users. Serum 2-AG levels were significantly higher in cannabis users than in controls. Cerebrospinal fluid anandamide correlated negatively with drug-free psychotic symptoms.

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**References**


**Fig. 1** Cerebrospinal fluid (CSF) anandamide levels across the three groups.
Online supplement

**Fig. DS1** Serum 2-arachidonoylglycerol (2-AG) levels across the three groups.
Cerebrospinal fluid anandamide levels, cannabis use and psychotic-like symptoms
Celia J. A. Morgan, Emma Page, Carola Schaefer, Katharine Chatten, Amod Manocha, Sumit Gulati, H. Valerie Curran, Brigitta Brandner and F. Markus Leweke
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Supplementary Material
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