TECHNICAL COMMENTARY

Endocannabinoids

Introduction

The endocannabinoid system is an endogenous biological system that regulates functions including cognition, sleep, energy metabolism, and inflammation. It modulates different neurotransmitter systems in the brain, including dopamine, glutamate, and GABA using two major lipid-based mediators, anandamide and arachidonoyl-sn-glycerol that act through type one and type two cannabinoid receptors.

Exogenous cannabinoids, such as delta-9-tetrahydrocannabinol (THC), the main psychoactive components of cannabis, and cannabidiol (CBD), impact on the endocannabinoid system. While disturbance of the endocannabinoid system after cannabis consumption has been associated with increased risk of psychotic illness, CBD alone has shown anti-inflammatory and antipsychotic properties.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. We also included reviews of psychotic disorders. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found one systematic review that met our inclusion criteria[3].

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Endocannabinoids

- Moderate to high quality evidence finds a large effect of higher concentrations of anandamide in the cerebrospinal fluid of patients, a medium-sized effect of higher concentrations of anandamide in the blood of patients, and a medium-sized effect of higher expression of type one cannabinoid receptors on peripheral immune cells of patients. There were insufficient usable data for a meta-analysis on type two cannabinoid receptors, and authors report mixed findings.
- Authors report that increased severity of positive and negative symptoms was associated with decreased anandamide levels in cerebrospinal fluid and increased expression of type one and two cannabinoid receptors in peripheral blood mononuclear cells. Poor cognitive performance was associated with decreased anandamide levels in serum and cerebrospinal fluid, increased expression of type one and two cannabinoid receptors in peripheral blood mononuclear cells, decreased expression of endocannabinoid system-synthesizing enzymes in peripheral blood mononuclear cells, and increased expression of endocannabinoid system-degrading enzymes in peripheral blood mononuclear cells.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Minichino A, Senior M, Brondino N, Zhang SH, Godwlewska BR, Burnet PWJ, Cipriani A, Lennox BR

Measuring Disturbance of the Endocannabinoid System in Psychosis: A Systematic Review and Meta-analysis

JAMA Psychiatry 2019; 76: 914-23

View review abstract online

Comparison	**Disturbance of the endocannabinoid system in people with psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) finds a large effect of higher concentrations of anandamide in the cerebrospinal fluid of patients, a medium-sized effect of higher concentrations of anandamide in the blood of patients, and a medium-sized effect of higher expression of type one cannabinoid receptors on peripheral immune cells of patients. There were insufficient data for a meta-analysis on type two cannabinoid receptors.** **Authors report that increased severity of positive and negative symptoms was associated with decreased anandamide levels in cerebrospinal fluid and increased expression of type one and two cannabinoid receptors in peripheral blood mononuclear cells. Poor cognitive performance was associated with decreased anandamide levels in serum and cerebrospinal fluid, increased expression of type one and two cannabinoid receptors in peripheral blood mononuclear cells, decreased expression of endocannabinoid system-synthesizing enzymes in peripheral blood mononuclear cells, and increased expression of endocannabinoid system-degrading enzymes in peripheral blood mononuclear cells.**

Anandamide and cannabinoid receptors

A large effect of higher concentrations of anandamide in the cerebrospinal fluid of patients;

5 studies, N = 611, SMD = 0.97, 95%CI 0.67 to 1.26, $p < 0.001$, $I^2 = 55\%$

Excluding one outlying study gave similar results and reduced heterogeneity to 0%.

There were no moderating effects of illness stage (prodromal, first-episode, and multi-episode), or of medication status (medicated, antipsychotic-free and antipsychotic-naïve), or whether patients were current users or nonusers of cannabis.

A medium-sized effect of higher concentrations of anandamide in the blood of patients; 8 studies, N = 647, SMD = 0.55, 95%CI 0.05 to 1.04, p = 0.03, I^2 = 90% Sequentially removing single studies consistently reduced heterogeneity, with the results remaining statistically significant. Larger SMDs were found when individuals with multi-episode and acute illness were compared with controls. *A medium-sized effect of higher expression of type one cannabinoid receptors on peripheral immune cells of patients;* 3 studies, N = 257, SMD = 0.57, 95%CI 0.31 to 0.84, p < 0.001, I^2 = 0% All studies included patients with multi-episode psychosis. No meta-analysis was conducted on type two cannabinoid receptors due to lack of data. *Increased severity of positive and negative symptoms was associated with;* Decreased anandamide levels in cerebrospinal fluid Increased expression of type one and two cannabinoid receptors in peripheral blood mononuclear cells *Poor cognitive performance was associated with;* Decreased anandamide levels in serum Decreased anandamide levels in cerebrospinal fluid Higher expression of type one and two cannabinoid receptors in peripheral blood mononuclear cells Reduced expression of endocannabinoid system-synthesizing enzymes in peripheral blood mononuclear cells Increased expression of endocannabinoid system-degrading enzymes in peripheral blood mononuclear cells

Consistency in results‡	Inconsistent, apart from peripheral immune cells
Precision in results§	Precise
Directness of results‖	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = probability of obtaining that result (p < 0.05 generally regarded as significant), SMD = standardised mean difference, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[4].

† Different effect measures are reported by different reviews.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium-sized effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[5]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large treatment effect[4].

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[6].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Minichino A, Senior M, Brondino N, Zhang SH, Godwlewska BR, Burnet PWJ*, et al.* (2019): Measuring Disturbance of the Endocannabinoid System in Psychosis: A Systematic Review and Meta-analysis. *JAMA Psychiatry* 76: 914-23.
4. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
5. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
6. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*