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Rochefort G, Provencher V, Castonguay-Paradis S, Perron J, Lacroix S, Martin C, Flamand N, Di Marzo V, Veilleux A. Intuitive eating is associated with elevated levels of circulating omega-3-polyunsaturated fatty acid-derived endocannabinoidome mediators. Appetite. 2021;156:104973.

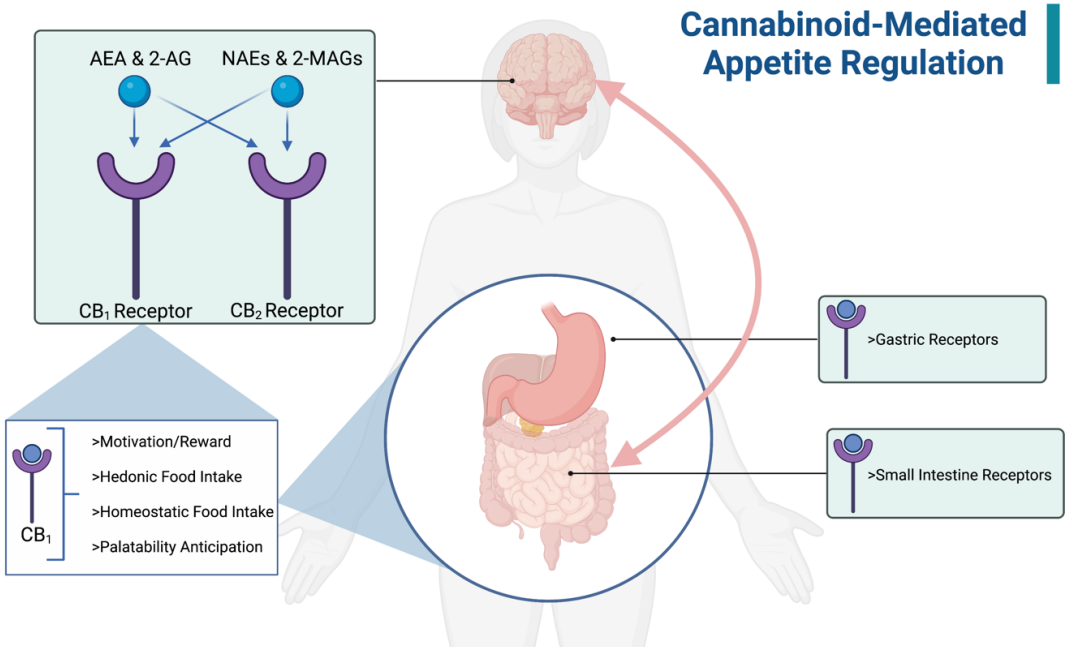
What We Know, Think We Know, or Are Starting to Know

There is major interest in the neurobiology of eating behaviour, and this area of research continues to expand our understanding of both external and internal factors that regulate energy intake [1,2]. The vast majority of nutrition research is dominated by a focus on external factors, e.g., portion control, meal regularity, food choice, physical activity [3].

However, there is increasing interest in shifting the emphasis to eating according to internal hunger and satiety cues. This area, broadly characterised as 'intuitive eating', emphasises 10 principles* [contained within four domains, i.e., subscales] to develop self-efficacy in eating according to internal cues, rather than emotional or situational stimuli [4]. In a previous Deepdive, we examined one of the first prospective cohort studies to evaluate intuitive eating behaviours and weight regulation in a cohort of young adults, which found that higher intuitive eating scores were associated with lower unhealthy weight control behaviours. Intervention studies also show lower levels of disinhibited eating [5].

The data so far from the limited prospective observational research, and from interventions, does suggest that intuitive eating may extend beyond behaviours, to underlying physiological correlates of these behaviours. What potential factors could explain the regulation of eating behaviour associated with intuitive eating?

In the neurobiology of eating behaviour, the endocannabinoid system has attracted interest [6,7]. Endocannabinoids are derived from polyunsaturated fats and are involved in regulation of appetite and energy homeostasis [6,7]. The endocannabinoid system contains two primary receptors, cannabinoid-1 and cannabinoid-2, which bind to circulating endocannabinoids synthesised from arachidonic acid, namely AEA, 2-AG, and their derivatives NAEs and 2-MAGs [6,7]. The cannabinoid-1 receptor has substantial mechanistic evidence indicating a role in energy regulation, appetite, and the balance of homeostatic/hedonic responsiveness to food, and receptors in the gut imply a potential bi-directional gut-brain relationship in regulating energy intake [8,9].



The present study analysed the associations between circulating levels of endocannabinoids and intuitive eating scores.

*Geek Box: Assessing Validity for Intuitive Eating

It is important to note that intuitive eating [lowercase] may refer to a measure of psychometric evaluation, and may refer to a specific intervention itself guided by the principles of Intuitive Eating [uppercase IE], as set out by Tribole and Resch.

The ten principles of IE include: i) reject the diet mentality; ii) honour your hunger; iii) make peace with food; iv) challenge the food police; v) respect your fullness; vi) discover the satisfaction factor; vii) honour your feelings without food; viii) respect your body; ix) exercise - feel the difference; x) honour your health. These 10 principles were initially clustered into three domains by Tylka, including: 1) unconditional permission to eat; 2) eating for physical rather than emotional cues; 3) reliance on hunger and satiety cues. These domains, and the principles contained therein, formed the basis of the first validated instrument to measure intuitive eating, the Intuitive Eating Scale [IES] [(10)].

Tylka et al. updated the domains of IE to include a 4th domain, that of body-food choice congruence. However, the original IES was validated in women only. Thus, in 2013 Tylka & Kroon Van Diest validated an updated version, the IES-2, which contains 23 items and included the body-food choice congruence domain and was validated in both sexes [(11)]*. Factor analysis, which identifies factors that correlate within the same person, confirmed the 4-domain construct of the IES-2. Cronbach's alpha, which is a measure of internal consistency for scale or test [over 0.70 is considered good consistency, >0.80 is stronger] for the IES-2 during validation was 0.89 and 0.87 for men and women, respectively. The IES-2 has also shown to be reproducible over time, albeit over a period of weeks [something to consider for prospective studies]. Thus, as an instrument used to assess intuitive eating in individuals, the IES-2 is a well-validated scale.*

The Study

190 participants [89 male, 101 female] were included in the final analysis. Participants completed three 24hr diet diaries, along with the full IES-2 to assess intuitive eating, and the Three-Factor Eating Questionnaire [TFEQ], which assess cognitive restraint, disinhibition, and hunger.

Participants attended the investigators' research facility after an overnight fast to have blood samples taken. Levels of several different NAEs and 2-MAGs were measured in the blood. To keep the Deepdive more concise, we will refer broadly to NAEs and 2-MAGs, rather than each individual metabolite.

The analysis compared scores on the IES-2 and TFEQ relative to tertiles of measured endocannabinoid levels, adjusting for BMI, age, and fatty acid intake [assessed from the average of the three 24hr recalls].

Results: Average age of the participants was 40yo for women and 42yo for men. 40/101 women and 49/89 men were classified according to BMI as overweight or obese, respectively.

- ***IES-2 Score by Sex and BMI*:** IES-2 scores were lowest in participants in the obese BMI category, and highest in participants in the normal BMI category. Certain sex differences were also observed, with men exhibiting higher scores for the IES-2 domain of eating for physical rather than emotional reasons.
- ***Circulating Cannabinoids & Eating Scales*:** Circulating levels of 2-MAGs were significantly associated with total IES-2 scores, and additionally associated with specific domains of the IES-2. There were no associations between any of the NAEs and the IES-2. The two

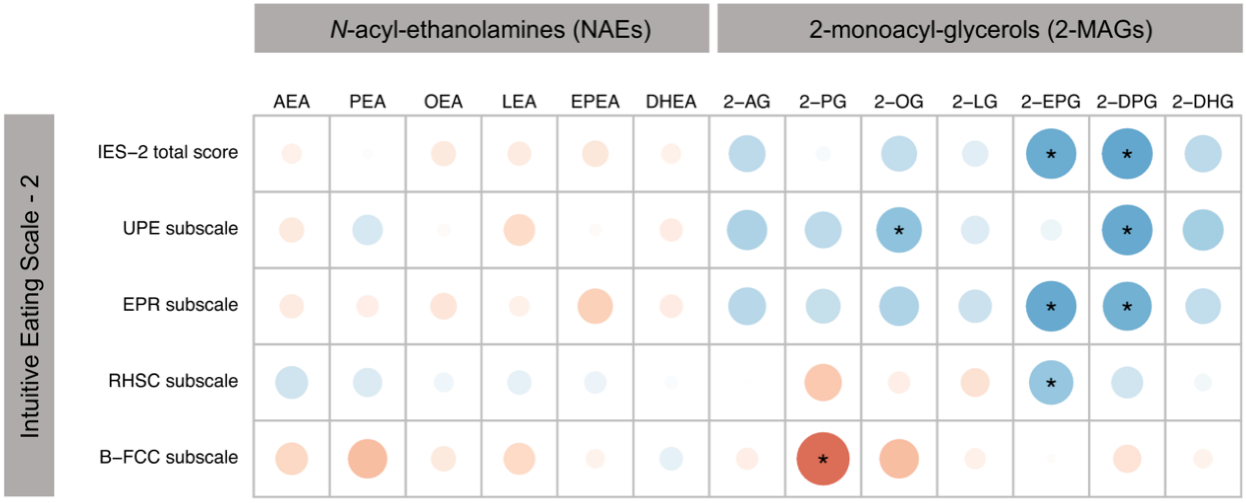


Figure from the paper illustrating a chart of associations between the NAEs [left side] and 2-MAGs [right side]; the boxes with a bold coloured circle and asterix in the circle indicate a significant association with the IES-2 scale. The top line of the table is the total IES-2 score, and each line of the table down from that is each of the four domains, or subscales, of the IES-2. Recall from the Geek Box above that these are 1) unconditional permission to eat [UPE]; 2) eating for physical rather than emotional cues [EPR]; 3) reliance on hunger and satiety cues [RHSC], and body-food congruence [B-FCC]. As is clear from this table, only 2-MAGs were significantly associated with IES-2 scores and scores within specific IES-2 domains.

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- ***Relationship Between Cannabinoids, BMI, and IES-2*:** IES-2 scores varied from highest to lowest across the three BMI categories of normal, overweight, and obese, respectively. In addition, IES-2 scores increased across tertiles of increasing circulating levels of 2-MAGs, i.e., higher IES-2 was associated with higher 2-MAGs levels. [more under ***Interesting Finding***, below].

The Critical Breakdown

Pros: The study had a decent sample size and was balanced for sex. Participants were otherwise healthy, with a wide range of BMI categories represented in the cohort. Advanced and accurate methods were used to assess body composition, i.e., DEXA scans, and for the measurement of blood cannabinoids [liquid chromatography/mass spectrometry]. The full IES-2 scale was used to assess intuitive eating, which allowed for each of the four domains to be analysed separately.

Cons: The lack of understanding of the direction of effect between cannabinoids and positive eating behaviours, e.g., intuitive eating, makes the correlational nature of this study more limited in the inferences possible from the results. Typical of much of the intuitive eating research, the majority of participants [89%] were Caucasian and well-educated. It remains unclear what the functional, mechanistic significance of elevated cannabinoids may be, further complicating making inferences from the study. Again, all science starts somewhere, and this is not a 'Con' *per se*, but it is always important to reiterate that these are correlational findings.

Key Characteristic

Any given study is only as good as current knowledge allows it to be. With this in mind, there is one crucial point through which this study must be placed in context: *we don't know the direction of effect between the associations observed in the present study*. In general, it is established that the direction of effect for cannabinoids is *increasing* hunger and hedonic responses to food [6,7]. And both NAEs and 2-MAGs are associated with *higher* body fat [12]. However, intuitive eating is associated with *positive* eating behaviours, maintenance of lower body weight, and lower binge eating [13,14]. So, are higher circulating 2-MAGs associated with *both* positive eating behaviours [i.e., IES-2] and hedonic food responses? The correlational nature of the present study leaves this question unresolved.

Interesting Finding

IES-2 scores were higher with increasing circulating levels of 2-MAGs, however, there was no statistical interaction between BMI and 2-MAG levels with IES-2 scores. This means that both associations – IES-2 scores with BMI and IES-2 scores with 2-MAG levels – were independent of each other.

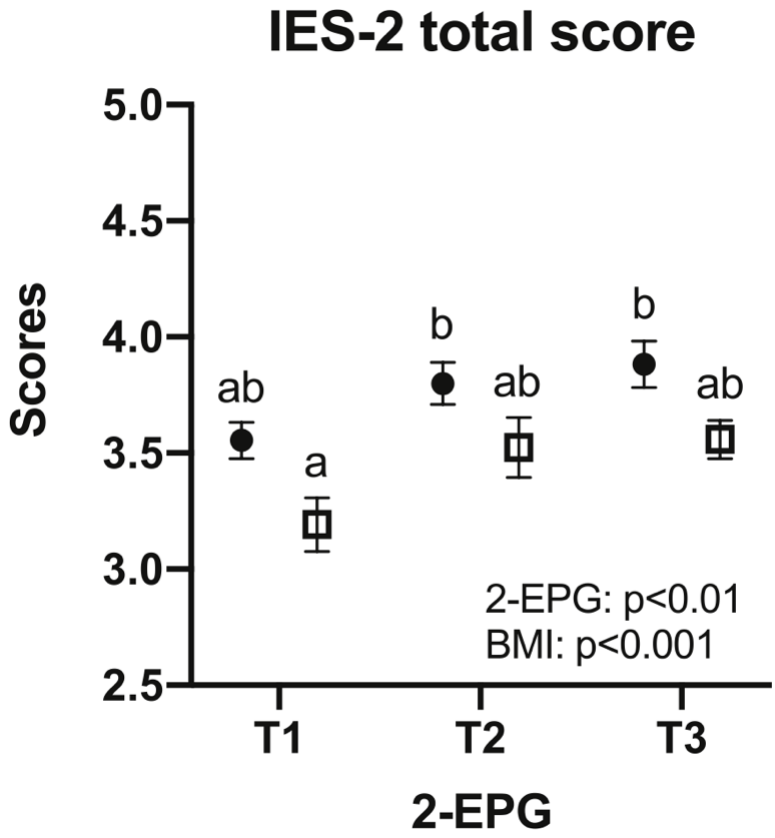

Figure *from the paper illustrating the relationship between tertiles of 2-EPG, the omega-3 derived 2-MAG [**x-axis, left to right**], and IES-2 scores [**y-axis**]. Black circles represent participants in the normal BMI category, while open squares represent participants in the overweight/obese BMI categories.*

As the graph above shows, in both normal BMI and overweight/obese BMI categories, increasing 2-EPG levels were associated with higher IES-2 scores. In participants in the normal BMI category, the baseline was higher, reflecting the fact that participants in this category had higher IES-2 scores compared to the other categories. Thus, the relationship between higher cannabinoids and IES-2 scores was independent of BMI [all categories showed this relationship].

This presents the puzzle for interpreting this study. In animals, blocking CB_1 receptors reduces motivation for fat and sweet foods [(15)]. Recall, however, that the 2-MAGs associated with IES-2 in the present study are derived from omega-3 fatty acids. Could it be that there is a relationship between these cannabinoids and the positive eating behaviours reflected in IES-2 scores, i.e., that perhaps these 2-MAGs are associated with more sensitivity to internal hunger cues? Maybe…the authors highlight that 2-EPG and 2-DPG may both act through non-CB_1 receptors, potentially meaning that they act through different pathways to other cannabinoids.

Relevance

The present study could be the first to show neural correlates of intuitive eating that may associate with regulation of the endocannabinoid system that exerts such a strong influence on appetite and food reward. Or it could be a red herring, because we don't fully understand the functions of the 2-MAGs that were associated with IES-2 in this study.

Teasing out cause-effect is a long way off in this research. For example, another recent study found that circulating levels of both NAEs and 2-MAGs were associated with higher body fat [12]. Specifically, NAEs were associated with higher subcutaneous fat, while 2-MAGs associated with greater visceral fat [12]. However, it is important to stress that the direction of the relationship between body fat and endocannabinoids has not been demonstrated, i.e., whether they are a product of adipose tissue or reflect some other processes [12].

This latter point is important for putting the present study into context. Recall from the ***Interesting Finding***, above, that both IES-2 scores were associated with higher 2-MAG levels, independent of BMI. Could it be that the omega-3 derived 2-MAGs influence homeostatic, rather than hedonic, pathways of energy intake regulation in the brain [and/or gut]? Maybe. This is one of the intriguing questions that are left to move forward with in future research.

So, what are we left with? Yes, cannabinoids are generally associated with increased appetite and hedonic food reward, known as the 'liking' part of the brain motivation-reward system [2]. Yes, there seem to be correlations between specific cannabinoids and both total body fat, and specific body fat depots [12]. And yes, we would perceive both of the above as 'negatives', however, intuitive eating is associated with *positive* eating behaviours, lower binge eating, dietary disinhibition, and lower unhealthy weight control behaviours [5,13,16]. Thus, the present study leaves us with an apparent paradox, for now.

Of course, this study could be interpreted to suggest that higher IES-2 scores are protective against the hedonic signalling of circulating endocannabinoids. Just a thought…I hate using this caveat: *more research needed!*

Application to Practice

With any intervention, there is a temptation to default to *"show me the mechanism"*. And we don't know what we don't know in relation to the potential physiological correlates of intuitive eating. Honestly, it also doesn't matter because *mechanism does not equal effect*. We have a plethora of human outcome data showing a benefit to the Intuitive Eating intervention, and other interventions that promote eating by internal cues [5,13,16]. And human outcomes will always come before mechanistic meanderings.

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