Genetic polymorphisms of the endocannabinoid system in obesity and diabetes

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The endocannabinoid system (ECS) is involved in many physiological processes including fertility, pain and energy regulation. The aim of this systematic review was to examine the contribution of single nucleotide polymorphisms (SNPs) of the ECS to adiposity and glucose metabolism. Database searches identified 734 articles, of which 65 were included; these covered 70 SNPs in genes coding for cannabinoid receptors 1 and 2 (CB1, CB2), fatty acid amide hydrolase (FAAH) and N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD). No studies included SNPs relating to monoacylglycerol lipase or diacylglycerol lipase. The CB1 receptor SNP rs1049353 showed 17 associations with lower body mass index (BMI) and fat mass (five studies). It also showed three associations with lower insulin levels (one study). Conversely, the CB1 receptor SNP rs1049353 showed 17 associations with lower body mass index (BMI) and fat mass (five studies). It also showed three associations with lower insulin levels (one study). Conversely, the CB1 receptor SNP rs1049353 was associated with increased BMI and waist circumference (two studies). The FAAH SNP rs324420 was associated with increased obesity (three studies). A haplotype of NAPE-PLD was associated with decreased BMI (one study). A total of 60 SNPs showed no association with any measured outcome. This review suggests a complex but important role of ECS SNPs in energy and glucose metabolism.

KEYWORDS

cannabinoid, diabetes, endocannabinoid, obesity, polymorphisms

INTRODUCTION

The endocannabinoid system (ECS) consists of two G-protein coupled receptors (CB1 and CB2) and endogenously produced ligands, or endocannabinoids such as anandamide and 2-arachidonoyl glycerol, and the enzymes involved in their synthesis or degradation: fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MAGL), diacylglycerol lipase (DAGL) and N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD). It is well established that CB1 activation leads to increases in energy storage which occur via increased motivation to consume food and to decreased satiety.

Single nucleotide polymorphisms (SNPs) are naturally occurring variations of a genetic sequence, which often affect protein structure. To date, studies on the effects of endocannabinoid SNPs have focused on central nervous system disorders such as Parkinson’s disease and Alzheimer’s disease. However, there is accumulating evidence for the role of endocannabinoid SNPs in adiposity and glucose metabolism. Therefore, the aim of this systematic review was to systematically collate the evidence relating to SNPs of the ECS in obese or diabetic phenotypes. By studying amino acid sequence alterations and any resultant residue changes, we hoped to identify important genetic changes that alter the normal physiology of adiposity and glucose metabolism.

MATERIALS AND METHODS

Searches were performed by two independent researchers using PubMed, EMBASE and Web of Science and concluded on January 26, 2018. Additional studies were identified from bibliographies. The search terms used were: Cannabinoid OR endocannabinoid receptor OR CB1 OR CB2 OR FAAH OR fatty acid amide hydrolase AND polymorphism AND obesity OR diabetes OR BMI OR monoacylglycerol lipase OR MAGL OR diacylglycerol lipase OR DAGL OR N-acyl phosphatidylethanolamine-specific phospholipase D OR NAPE-PLD. A summary of search results and exclusions is given in Supporting Information Figure S1, and a full reference list is available in Appendix S1.
The SNP database dbSNP was used to gather information regarding nucleotide and amino acid changes. Articles included were original studies relating to polymorphisms of the ECS affecting energy regulation, glucose homeostasis and adiposity. Demographic and clinical parameters included were: body mass index (BMI); waist circumference (WC); waist-to-hip ratio (WHR); body weight; adiposity; type II diabetes mellitus (T2DM); insulin and glucose levels; homeostatic model assessment for insulin resistance (HOMA$_{IR}$); adipokine levels (adiponectin, leptin and resistin); cardiovascular parameters (blood pressure, heart rate); inflammation (levels of interleukin 6 [IL-6], tumour necrosis factor alpha [TNFα] and C-reactive protein [CRP]); and lipid levels (triglycerides, HDL-C and LDL-C). Records excluded were review articles, articles on the ECS not relating to polymorphisms, studies regarding central disorders, studies in non-humans and studies in a language other than English.

Included articles were analysed for significant ($P < 0.05$) positive or negative associations between SNPs and relevant parameters. A “positive” association refers to a higher value of the measured outcome in the presence of the polymorphism, whereas a “negative” association refers to a lower value in the presence of the polymorphism. The absence of a significant association between the measured outcome and the polymorphism is described as a “neutral” association. Risk of bias was assessed using the Cochrane Collaboration’s tool for assessing risk of bias.

3 | RESULTS

A total of 65 studies were identified from among 733 full-text articles. Risk of bias in these studies was low overall and is summarized in Supporting Information Figure S2. In total, 38 CB$_1$, 18 CB$_2$, 13 FAAH and one NAPE-PLD SNPs were studied. No studies relating to MAGL or DAGL SNPs were found. The most commonly studied SNPs, and those that showed the most significant associations, were CB$_1$ SNPs rs1049353 and rs806368, and FAAH SNP rs324420. Their associations with body weight and glucose metabolism parameters are presented in Table 1. All SNPs and their associations with measured outcomes are documented in Supporting Information Table S1. A summary of all included studies and their relevant findings is shown in Supporting Information Table S2.

3.1 | BMI and body weight

3.1.1 | CB$_1$

The rs1049353 mutant allele was associated with lower BMI in six European populations and with decreased fat mass in a Danish population ($n = 783$). Conversely, homozygosity for the rs1049353 mutant allele was associated with higher WHR and WC in obese men ($P < 0.01$; $n = 1064$) and with increased childhood obesity in a European population ($P = 0.01$; $n = 200$). The majority of associations with rs1049353 were neutral (90%) (Table 1). However, negative associations were more common than positive associations (Figure 1), suggesting that this SNP plays a part in a more complex genetic susceptibility to increased adiposity. Male carriers of the rs806368 mutant allele showed greater BMI values in a Japanese cohort ($P = 0.001$) and were more likely to be obese ($P = 0.01$; $n = 1452$) (Supporting Information Table S1).

3.1.2 | FAAH

FAAH polymorphism rs324420 was positively associated with obesity in four cohorts ($n = 18,987$).

3.1.3 | CB$_2$

The mutant allele of CB$_2$ SNP rs3123554 was associated with lower total body fat in women but not men, in a European cohort ($P = 0.001$), with lower BMI in individuals at risk of T2DM ($P < 0.01$) and with reduced weight loss ($P < 0.01$; $n = 2006$).

3.1.4 | NAPE-PLD

In a Norwegian cohort, a haplotype of NAPE-PLD showed an association with increased BMI ($P < 0.05$; $n = 5011$).

3.2 | Type II diabetes

3.2.1 | CB$_1$

The mutant allele of CB$_1$ polymorphism rs1049353 was associated with lower insulin, glucose and HOMA$_{IR}$ levels in Spanish obese women and with lower insulin in two other European cohorts ($n = 983$). CB$_1$ SNP rs806365 was associated with decreased HOMA$_{IR}$ values and with incidence of T2DM in a North American cohort ($P < 0.05$; $n = 2411$).

3.2.2 | CB$_2$

The mutant allele of CB$_2$ polymorphism rs3123554 was associated with raised insulin levels and with HOMA$_{IR}$ values in an obese population ($n = 1027$) (Figure 1).

3.2.3 | FAAH

The mutant allele of FAAH polymorphism rs324420 was associated with lower insulin levels in two obese populations ($P < 0.05$; $n = 165$), and was also associated with lower HOMA$_{IR}$ levels in obese Spanish females ($P < 0.05$; $n = 143$).

3.3 | Lipids

Overall, 22 positive associations with lipid levels were seen. The mutant allele of CB$_1$ SNP rs1049353 was associated with higher HDL and lower TGs in three cohorts, as well as with lower TGs in two populations ($n = 808$). FAAH SNPs rs324420 and rs3123554 were associated with higher TG levels in European cohorts ($P < 0.05$; $n = 1644$) (Table 1). FAAH SNP rs324420 was also associated with raised anandamide levels in a Brazilian population ($P < 0.05$; $n = 200$).

4 | DISCUSSION

The aim of this study was to collate evidence relating to SNPs of the ECS and obese or diabetic phenotypes to identify important genetic
changes that alter metabolism. From among the 65 included articles, 70 polymorphisms were studied. CB1 SNP rs1049353 showed 17 associations with lower BMI and fat mass. It also showed associations with reduced glucose, insulin and HOMAIR values. CB1 polymorphism rs806368 showed five associations with increases in BMI, WC and WHR. The FAAH SNP rs324420 showed seven associations with increased incidence of obesity. A total of 60 SNPs showed no association with any measured outcome. These findings suggest an important role of selected SNPs of the ECS in adiposity, although the number of studies showing no associations means that their contribution is probably part of complex interactions.

The SNP rs1049353 occurs at nucleotide position 1359, a region of the CB1 (CNR1) gene coding for the receptor’s intracellular domain or C-terminal. One study showed that replacement of the C-terminal resulted in decreased affinity of the CB1 agonist CP55940 and increased affinity of the CB1 antagonist SR141716A. This suggests that the C-terminal is important in receptor signalling. Although rs1049353 is a synonymous SNP and does not result in a change in amino acid residue (Thr>Thr), altered substrate interaction deriving from synonymous SNPs has been observed elsewhere, suggesting that this is a legitimate theory.

The literature showed 13 associations between rs1049353 and reductions in parameters of glucose metabolism (Table 1). This suggests that this SNP is important in diabetic phenotypes, probably caused by upregulation of gluconeogenic transcription factors as the result of increased CB1 receptor activity. It is unclear why many studies (n = 14) showed no association with parameters of glucose metabolism.

The rs324420 SNP reduces FAAH activity and increases the likelihood of the enzyme itself being degraded, leading to cannabinoid

| Polymorphism | Gene   | Nucleotide change | Nucleotide position | Region of gene | Amino acid change | Amino acid position | Associations |
|--------------|--------|------------------|---------------------|----------------|------------------|-------------------|--------------|
| rs1049353    | CNR1   | G>A              | 1359                | Exon           | Thr>Thr          | 453               | Positive:  |
|              |        |                  |                     |                |                  |                   |  |
|              |        |                  |                     |                |                  |                   | • Homozygosity for mutant allele associated with increased WHR and WC in obese men only. |
|              |        |                  |                     |                |                  |                   | • Mutant allele associated with higher fat in post-menopausal women. |
|              |        |                  |                     |                |                  |                   | • Mutant allele associated with increased BMI in T2DM subjects. |
|              |        |                  |                     |                |                  |                   | • Wild-type allele associated with higher HOMAIR. |
|              |        |                  |                     |                |                  |                   | • Mutant allele group associated with greater weight loss and decrease in BMI. |
|              |        |                  |                     |                |                  |                   | • Mutant allele associated with childhood obesity. |

Negative:  |

• Mutant allele associated with lower glucose. |
• Mutant allele associated with lower insulin. |
• Mutant allele with lower BMI. |
• Mutant allele with lower HOMAIR, TGs. |
• Mutant allele with lower BMI, WC and obesity. |

| rs806368    | CNR1   | T>C              | 4895                | Intron         | -                | -                 | Positive:  |
|            |        |                  |                     |                |                  |                   |  |
|            |        |                  |                     |                |                  |                   | • Mutant allele associated with increased WHR. |
|            |        |                  |                     |                |                  |                   | • Mutant allele associated with increased TGs. |
|            |        |                  |                     |                |                  |                   | • Mutant allele associated with increased BMI, WC and obesity. |

Positive:  |

• Mutant allele associated with higher insulin and HOMAIR in patients without MetS. |
• Homozygosity for mutant allele associated with increased BMI. |
• Mutant allele associated with obesity. |
• Wild-type allele associated with childhood obesity. |
• Mutant allele associated with increased TGs. |

Negative:  |

• Mutant allele associated with lower TGs, glucose and HOMAIR levels. |
• Mutant allele associated with better percentage weight loss 9 months and 1 year after bariatric surgery, but not after 3 months. |
• Lower insulin and HOMAIR in mutant-type group. |
• Mutant allele associated with greater decreases in weight and WC than wild-type following hypocaloric diet. |
• Mutant allele also associated with greater decreases in glucose, HOMAIR and TGs. |
• Wild-type allele associated with lower WC, BMI, HOMAIR and TGs in subjects with MetS. |
• Mutant allele associated with lower insulin, glucose and HOMAIR values. |

Abbreviations: BMI, body mass index; CNR1, cannabinoid receptor gene 1; FAAH, fatty acid amide hydrolase; HOMAIR, homeostatic model assessment of insulin resistance; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; TGs, triglycerides; TNF-α, tumour necrosis factor α; WC, waist circumference; WHR, waist-to-hip ratio.
Similarly, the associations between the CNR2 polymorphism overactivity. Subsequent CB₁ activation leads to adipogenesis and reduced expenditure, all of which contribute to obesity-related phenotypes. Our analysis showed that rs324420 was associated with higher anandamide levels, increased BMI and obesity,7,25,30,31 which suggests cannabinoid over-activation and subsequent adiposity and that this SNP, therefore, reduces FAAH activity (Table 1).

The potential contribution of CNR2 polymorphisms to human metabolism is less clear. Fewer studies investigated these SNPs, and the two polymorphisms studied (rs3123554 and rs35761398) showed conflicting associations with body weight parameters and glucose metabolism. As CB₂ receptors are found primarily in the central nervous system and on immune cells, it is likely that they are less involved in the regulation of body fat and, therefore, any alterations in their genetic structure are less relevant here. As no studies were found relating to SNPs of DAGL or MAGL, their contribution to obesity and glucose metabolism remains unclear.

Increasing age may determine the impact of the polymorphism. For instance, associations between SNPs rs2023239 and rs806381 and increased anthropometric measurements were found only in adult subjects.46,47 Ageing leads to reductions in ligand binding and coupling between the CB₁ receptor and its G-protein,49 which may account for the delayed onset of increases in body weight parameters in some populations. There may also be an impact of gender on these data. Male carriers of the mutant alleles of CNR1 polymorphisms rs1049353 and rs806368 have an increased likelihood of obesity.7,25 Similarly, the associations between the CNR2 polymorphism rs3123554 and lower BMI, weight and body fat percentage were reported in women.40 Gender differences in feeding behaviour have been observed previously in animal models.13 This may be explained by the action of oestrogen, which uncouples CB receptors from their effector systems in synaptic terminals, thus reducing the effect of cannabinoids.50 Higher oestrogen levels in non-pregnant females may therefore contribute to these gender-specific findings.

In conclusion, associations between the mutant allele of the CB₁ SNP rs1049353 and decreased fat mass, weight and BMI indicate that this SNP is an important contributor to alterations in metabolism. Evidence indicates that decreased receptor functionality affects normal pathways of adipogenesis and energy regulation. Its effects also extend to improvements in lipid levels and parameters of glucose metabolism. The mutant allele of FAAH polymorphism rs324420 was associated with increased BMI and triglyceride levels, possibly caused by decreased enzyme activity and overactivation of the ECS. Other SNPs had varying associations, but results were often conflicting. These findings represent therapeutic targets for the management of obesity and hyperlipidaemia, and assessment of patients for these genetic changes would provide an opportunity to provide personalised treatment for a proportion of patients. Further studies in populations of varying demographics are needed, to investigate the role that other SNPs play in adiposity and glucose metabolism, as well as genetic studies to determine the molecular changes of the SNPs responsible for alterations in function.
Conflict of interest
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Author contributions
J. M. D. was responsible for search terms, conducting initial literature searches, gathering relevant data from articles, writing the majority of the manuscript, construction of the tables and figures and performing referencing throughout. S. A. M. performed a second literature search, confirmed the findings, helped in writing and editing the manuscript, produced graphs using data gathered and contributed to referencing. I. I. helped in editing the manuscript, suggested alterations to tables and provided assistance in the publishing and proofing process. S. E. O. suggested search terms and databases to use, provided guidance, edited the manuscript and assisted in the publishing process.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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