A Human Fatty Acid Amide Hydrolase (FAAH) Functional Gene Variant Is Associated With Lower Blood Pressure in Young Males

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BACKGROUND
Fatty acid amide hydrolase (FAAH) inhibitors, preventing endocannabinoid (EC) degradation, reduce blood pressure (BP) and heart rate in young male (YM) hypertensive rodents. The functional human FAAH 129T gene variant results in reduced protein level and enzymatic activity but its relationship with BP is unknown. This study investigates the relationship among FAAH P129T alleles and cardiovascular features in YMs at baseline and after 9-year follow-up, and in older male obese hypertensive (OH) patients, in whom the EC system (ECS) is overactive.

METHODS
Genotype analysis was performed in 215 Caucasian male students (24 (0.2) years old) and in 185 older OH patients (50 (0.2) years old). YMs were also followed up for 9 years. Clinical and anthropometric variables, BP, cardiac and carotid artery echographic measurements were evaluated.

RESULTS
YMs with the FAAH 129T allele had lower systolic (P = 0.042) and mean BP (P = 0.022), and a trend toward lower diastolic BP (P = 0.06). Such significant association was maintained at follow-up. In contrast, the same allele was not associated with BP in older OH. No association was found with other cardiac and vascular variables.

CONCLUSION
An FAAH defective gene variant results in lower BP in YMs, similar to the findings in young rodents. This effect is lost in older OH patients. Because cannabinoid CB1 receptor blockade is associated with BP reduction in OH patients, EC effects and the use of ECS-interfering drugs is likely to be age and clinical-condition dependent.


Endocannabinoid system (ECS) contributes to regulation of energy balance and glucose/lipid metabolism through central1 and peripheral activities.2,3 Indeed, obesity is associated with a marked increase in adipose tissue and circulating endocannabinoids (EC)4,5 and ECS dysregulation contributes to the development of metabolic and cardiovascular complications.6 Moreover, ECS might play a relevant role also in blood pressure (BP) regulation and in cardiovascular diseases.7 Disappointingly, the effects of EC in the cardiovascular system appear somewhat contradictory,8,9 depending on experimental conditions, animal species, and, in human, by clinical background. Indeed, EC reduced BP through CB1 receptor in anesthetized but not in conscious animals, and in spontaneously hypertensive rats after acute administration.9 Experimental studies, usually performed with young male (YM) animals, showed that EC had a hypotensive effect in rodent models of hypertension and under conditions of endotoxic/hemorrhagic shock.9 In contrast, CB1 blockade was associated with reduction in body weight and BP in Rimonabant In Obesity trials.10 This hypotensive effect was more evident in obese hypertensive (OH) patients treated with antihypertensive drugs and in diabetics with BP ≥130/85 mm Hg. Based on these data, we hypothesized7 that higher EC levels reduce BP in lean YMs whereas the over-active ECS of obese subjects induces so many metabolic alterations that the hypotensive effect of EC is overridden and, on the contrary, CB1 blockade does not hinder weight-loss related decrease in BP.

An important component of the ECS is fatty acid amide hydrolase (FAAH), one of the main enzymes responsible for EC degradation in vivo.3 It has been proposed as a promising target for modulating EC signaling, with therapeutic potential in anxiety, hypertension, and inflammatory disorders. In hypertensive rats, an FAAH inhibitor (URB597) decreased BP to near-normotensive values by decreasing cardiac contractility and peripheral resistance. Similarly, inhibitors of the anandamide uptake induced greater BP reduction in hypertensive than normotensive animals, by increasing anandamide concentrations at the receptor level.9

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In vivo, higher EC levels might be due to defective genetic variants of FAAH. Indeed, the human FAAH C385A single-nucleotide polymorphism (rs324420) induces a P129T amino-acid substitution and the 129T variant is characterized by reduced protein level and enzymatic activity. In this context, lean YM carriers of the 129T allele might have higher EC levels and lower BP, whereas OH patients might have a further EC overactivity with unclear effects on BP.

This study aimed at investigating whether the FAAH P129T gene variant is associated with cardiovascular effects in YM participants of the Ancona Heart Doctor Study (AHDS) and in an older population of male OH patients. To further study the possible effect of 129T FAAH variant in YMs, we also analyzed clinical parameters of a subset of YMs who underwent 9 years of follow-up.

METHODS

The study protocol was reviewed and approved by local ethical committee and written informed consent was obtained from all subjects. The study involved 215 YM participants of the AHDS (114 of them underwent also 9-year follow-up (YM-fup)), and 185 OH patients.

The protocol of the AHDS was previously described. In brief, we recruited YMs without previously diagnosed cardiovascular diseases. Family history of hypertension, smoking habits, and physical activity were carefully evaluated. Height, weight, waist and hip circumferences, sitting systolic and diastolic BP (SBP and DBP, respectively; mean of three measurements with a mercury sphygmomanometer), and heart rate were measured by a physician. Cardiac dimensions and carotid intima-media thickness were also measured by echocardiography and Doppler ultrasonography. Left ventricular mass (LVM) was calculated and indexed both by body surface area (LVMi) and by height\(^2\) (LVM/h\(^2\)).

A total of 114 YMs underwent 9-year follow-up (mean age 32.3 ± 2.4 years) and were revaluated with the same protocol (clinical and instrumental measurements).

Male OH participants in this study (≤65 years) were recruited from our “Hypertension Excellence Centre” (of the European Society of Hypertension) and represented a larger sample of a population already described. Obesity was defined as BMI ≥30 kg/m\(^2\). Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or current antihypertensive therapy. Secondary forms of hypertension were excluded. Blood was drawn after an overnight fast to measure glucose and lipid profiles.

To confirm this association, we analyzed available data coming from the 9-year follow-up of the AHDS (Table 1). YM-fup showed a significant increase in BMI (from 23.7 to 25.1 kg/m\(^2\)), waist (from 83.1 to 90.7 cm), and LVM (LVMi from 33.3 to 103.9 g/m\(^2\)), the latter being a likely consequence of the increased BMI/waist. In contrast, significant decrease in SBP (from 128.0 to 119.0 mm Hg), MBP (from 95.9 to 92.3 mm Hg), and heart rate (from 75.9 to 70.2 mm Hg) were observed. Despite these changes, the association between FAAH 129T allele and lower BP was strictly preserved (Table 1). Indeed, after 9 years, we still found significantly lower SBP (115.9 vs. 121.1 mm Hg, \(P = 0.024\)) and MBP (90.3 vs. 93.8 mm Hg, \(P = 0.022\)) and a trend toward lower DBP (80.1 vs. 77.6 mm Hg, \(P = 0.08\)) in YM carriers of the FAAH 129T allele.

Finally, no FAAH genotype-related difference in BP was found in OH patients, even after adjusting for antihypertensive therapy. Moreover, we did not find any association with the lipid profile of OH patients. In both populations, we did not find any association between FAAH genotypes and cardiac (Table 1) or vascular variables (data not shown).

DISCUSSION

ECS has been related to BP regulation and heart function. The prevailing concept, based mostly on mouse and rat models and using young animals, is that the ECS is relevant for the cardiovascular system particularly in hypertension, in which it lowers BP.

In this study, YM carriers of the FAAH 129T gene variant had lower BP and the difference in SBP between YMs with or without FAAH wild-type allele was very relevant: ~4 mm Hg (Table 1). A similar trend was observed for DBP and MBP.
where MBP reached statistical significance. Moreover, we were able to confirm this association using available data at 9-year follow-up of the AHDS, despite aging-related differences in anthropometrics, BP, and cardiac dimensions. The overall reduction in BP levels after 9 years of follow-up in YMs deserves further consideration. Indeed, we were surprised by this finding, also because methodological bias was very unlikely: BP was measured using a mercury sphygmomanometer by trained physicians in both visits. Therefore, the most likely explanation was a different reactivity to BP measurement (white-coat effect) between previous medical students at their first experience with the “inflated cuff” (higher reactivity) and physicians familiar with BP measurement (lower-than-average reactivity). The significantly lower heart rate at the follow-up visit supports this interpretation. Because FAAH 129T is a defective variant that might be associated with higher EC levels, our results are in agreement with published data on animal models that are usually performed with YM rodents in which the FAAH 129T allele might indeed have higher EC levels and lower BP.

Cannabinoids appear to induce a negative inotropic effect on human myocardium, but we did not observe significant associations among FAAH alleles and cardiac or vascular parameters. The lack of this association in YMs should be considered in the context of the population studied. Indeed, the effect associated with FAAH variants is within the range of normal BP that characterized this young healthy population. There are no available data about the association between differences within the normal BP range and lower LVM in YMs. In this context, a functional hemodynamic resetting between heart and the circulation could result mainly in lower SBP without significantly reducing LVM. Finally, we did not find any association between the FAAH variant, BMI, and waist circumference, contrary to a previous report, but according to recent data obtained in 5,801 Danish subjects.

The lack of association between FAAH 129T allele and lower BP in OH patients suggests that reduction in FAAH activity, followed likely by an increase in EC levels, did not lower BP in older OH patients. The different FAAH effect on BP in YM vs. OH patients suggests that reduction in FAAH activity, possibly followed by an increase in EC levels, did not lower BP in older OH patients. The different FAAH effect on BP in YM vs. OH patients suggests that reduction in FAAH activity, followed likely by an increase in EC levels, did not lower BP in older OH patients. The different FAAH effect on BP in YM vs. OH patients suggests that reduction in FAAH activity, followed likely by an increase in EC levels, did not lower BP in older OH patients. The different FAAH effect on BP in YM vs. OH patients suggests that reduction in FAAH activity, followed likely by an increase in EC levels, did not lower BP in older OH patients. The different FAAH effect on BP in YM vs. OH patients suggests that reduction in FAAH activity, followed likely by an increase in EC levels, did not lower BP in older OH patients. The different FAAH effect on BP in YM vs. OH patients suggests that reduction in FAAH activity, followed likely by an increase in EC levels, did not lower BP in older OH patients.

## Table 1 | Clinical parameters of the young and older obese hypertensive males according to FAAH genotypes

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>YMs (n = 215)</th>
<th>FAAH 129P (n = 149)</th>
<th>FAAH 129T (n = 66)</th>
<th>P</th>
<th>YMs (n = 114)</th>
<th>FAAH 129P (n = 76)</th>
<th>FAAH 129T (n = 38)</th>
<th>P</th>
<th>OH (n = 185)</th>
<th>FAAH 129P (n = 142)</th>
<th>FAAH 129T (n = 43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.0 (0.2)</td>
<td>23.7 (0.2)</td>
<td>24.7 (0.3)</td>
<td>0.014</td>
<td>32.3 (0.2)*</td>
<td>32.4 (0.3)</td>
<td>32.5 (0.4)</td>
<td>0.74</td>
<td>50.0 (0.7)</td>
<td>49.7 (0.83)</td>
<td>50.7 (1.5)</td>
<td>0.59</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 (0.2)</td>
<td>23.9 (0.2)</td>
<td>23.9 (0.3)</td>
<td>0.36</td>
<td>25.1 (0.3)*</td>
<td>25.1 (0.3)</td>
<td>25.1 (0.5)</td>
<td>0.90</td>
<td>33.3 (0.3)</td>
<td>33.4 (0.39)</td>
<td>33.2 (0.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>83.1 (0.5)</td>
<td>83.7 (0.6)</td>
<td>81.8 (0.9)</td>
<td>0.08</td>
<td>90.6 (0.8)*</td>
<td>90.7 (0.9)</td>
<td>91.1 (1.3)</td>
<td>0.79</td>
<td>110.0 (1.0)</td>
<td>110.1 (0.75)</td>
<td>110.1 (1.3)</td>
<td>0.96</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>128.0 (0.9)</td>
<td>129.5 (1.1)</td>
<td>125.5 (1.6)</td>
<td>0.042</td>
<td>119.0 (1.1)*</td>
<td>121.1 (1.3)</td>
<td>115.9 (1.8)</td>
<td>0.024</td>
<td>145.8 (1.5)</td>
<td>144.8 (1.84)</td>
<td>149.1 (3.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>79.8 (0.6)</td>
<td>80.8 (0.7)</td>
<td>78.4 (1.1)</td>
<td>0.06</td>
<td>78.9 (0.7)</td>
<td>80.1 (0.8)</td>
<td>77.6 (1.1)</td>
<td>0.08</td>
<td>93.3 (1.0)</td>
<td>93.2 (1.24)</td>
<td>94.7 (2.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>MDP (mm Hg)</td>
<td>95.9 (0.6)</td>
<td>97.0 (0.7)</td>
<td>94.1 (1.1)</td>
<td>0.023</td>
<td>92.3 (0.8)*</td>
<td>93.8 (0.9)</td>
<td>90.3 (1.2)</td>
<td>0.022</td>
<td>110.2 (1.1)</td>
<td>110.0 (1.30)</td>
<td>112.2 (2.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>75.9 (1.0)</td>
<td>75.9 (0.9)</td>
<td>75.4 (1.4)</td>
<td>0.77</td>
<td>70.2 (1.1)*</td>
<td>69.4 (1.4)</td>
<td>70.1 (2.0)</td>
<td>0.75</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>93.3 (1.1)</td>
<td>93.1 (1.3)</td>
<td>93.3 (2.0)</td>
<td>0.94</td>
<td>103.9 (2.0)*</td>
<td>102.8 (2.4)</td>
<td>105.5 (3.3)</td>
<td>0.52</td>
<td>128.3 (2.6)</td>
<td>126.3 (3.47)</td>
<td>127.9 (5.9)</td>
<td>0.82</td>
</tr>
<tr>
<td>LVM/h².7 (g/m²)</td>
<td>38.5 (0.5)</td>
<td>38.3 (0.6)</td>
<td>38.8 (0.9)</td>
<td>0.67</td>
<td>42.3 (0.9)*</td>
<td>41.7 (1.1)</td>
<td>43.6 (1.5)</td>
<td>0.31</td>
<td>64.2 (1.4)</td>
<td>62.4 (1.84)</td>
<td>63.8 (3.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Total cholesterol³ (mg/dl)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>206.5 (3.4)</td>
<td>208.1 (4.43)</td>
<td>197.5 (7.9)</td>
<td>0.25</td>
</tr>
<tr>
<td>HDL cholesterol³ (mg/dl)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>41.0 (0.7)</td>
<td>41.7 (0.82)</td>
<td>39.3 (1.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Triglycerides³ (mg/dl)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>176.9 (8.7)</td>
<td>163.5 (8.78)</td>
<td>158.7 (15.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>LDL cholesterol³ (mg/dl)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>130.1 (2.9)</td>
<td>118.9 (5.38)</td>
<td>117.5 (9.8)</td>
<td>0.90</td>
</tr>
<tr>
<td>Glycemia (mg/dl)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>103.3 (2.6)</td>
<td>104.0 (3.00)</td>
<td>102.2 (5.2)</td>
</tr>
</tbody>
</table>

Data are mean and s.e. Analysis of variance (ANOVA) adjusted for covariates (see Methods).

BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; LVM/h².7, left ventricular mass indexed by height².7; LVMi, left ventricular mass indexed by body surface area; MBP, mean blood pressure; OH, obese hypertensive; SBP, systolic blood pressure; YM, young male.

³Patients on active treatment with statins or fibrates (n = 20) were excluded. *P < 0.01 vs. basal evaluation (ANOVA for repeated measures).
of intra-abdominal adiposity. In any case, the treatment with the selective CB1-blocker rimonabant (20 mg/day) can reduce BP in obesity, particularly in OH patients with higher BP at baseline and/or treated with antihypertensive medications, in addition to its main effect on body weight reduction. 10

In summary, we confirm that a FAAH variant with reduced enzymatic activity associates with lower BP in healthy YMs, as previously described in young, male, non-obese rodents. 9 In contrast, the presence of the FAAH variant with lower enzymatic activity did not appear to induce any effect on BP in older OH subjects. As BP reduction in such kind of patients is evident after CB1 blockade treatment, 10 our data indirectly support the use of CB1 blockers in older OH patients. In the context of obesity, an overactive ECS could behave differently and have harmful effects when compared to young rodents or humans. In conclusion, our results, based on the association with a functional FAAH variant, validate the hypotensive effect of EC on human young healthy subjects and suggest that the effects of ECS and its blockers likely depend on age and clinical/metabolic condition.

Disclosure: The authors declared no conflict of interest.