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The faecal abundance of short chain fatty acids is increased in men with a non-dipping blood pressure profile

Justine Huart[a,b]*, Arianna Cirillo[c]*, Annie Saint-Remy[a], Jean-Marie Krzesinski[a,b], Pascal de Tullio[c]† and François Jouret[a,b]†

[a]Division of Nephrology, University of Liège Hospital (ULiège CHU), ULiège, Liège, Belgium; [b]Groupe Interdisciplinaire de Génoprotéomique Appliquée (GIGA), Cardiovascular Laboratory of Translational Research in Nephrology (LTRN), ULiège, Liège, Belgium; [c]Center for Interdisciplinary Research on Medicines (CIRM), Metabolomics group, ULiège, Liège, Belgium

ABSTRACT

Background and aims: Gut microbiota (GM) has been involved in the pathophysiology of hypertension (HT), notably *via* short chain fatty acids (SCFAs). Among the clinical manifestations of HT, the absence of a significant drop in night-time blood pressure (BP) (also known as the non-dipping BP profile) has been associated with poor renal and cardiovascular outcomes. The putative link between GM-derived metabolites and BP dipping status is still unknown.

Methods: Male volunteers ($n = 44$) were prospectively subjected to 24-hour ambulatory blood pressure monitoring, stool sample collection and a medical questionnaire. Metabolomics analyses of stool samples were conducted using Nuclear Magnetic Resonance (NMR).

Results: Higher amounts of acetate, butyrate and propionate were found in the stools of non-dippers ($n = 12$) *versus* dippers ($n = 26$) ($p = 0.0252$, $p = 0.0468$, and $p = 0.0496$, respectively; $n = 38$ *in toto*). NMR spectral data were not interpretable in 5 dippers and 1 non-dipper. A similar significant association was found when including only patients without anti-HT medications ($p = 0.0414$, $p = 0.0108$, and $p = 0.0602$, respectively; $n = 21$ *in toto*). A not significant trend was observed when focussing only on HT patients without anti-HT medications ($p = 0.0556$; $n = 14$ *in toto*).

Conclusion: Our pilot study highlights a putative link between GM-derived SCFAs and the BP dipping status, independently of the BP status itself or the anti-hypertensive medications.

Introduction

Gut microbiota (GM) has been involved in the pathophysiology of hypertension (HT), possibly *via* its role in the production of short chain fatty acids (SCFAs) from diet carbohydrate fermentation [1]. We and others have recently reported on significant correlations between the 24h mean blood pressure (BP) levels and the entire stool metabolome, as well as between BP levels and the faecal abundance of bacteria belonging to the *Clostridial* order. Higher amounts of the 3 main SCFAs (i.e. acetate, butyrate and propionate) have been also found in the stools of patients with HT compared to normotensive (NT) controls [2,3]. The absence of a significant drop in night-time BP (also known as the non-dipping BP profile) measured by 24-hour ambulatory BP monitoring (24h-ABPM) has been associated with poor renal and cardiovascular outcomes,

independently of HT [4]. In our previous study, no significant difference in GM composition was observed between dippers *versus* non-dippers [2]. However, we did not compare the faecal metabolome of dippers *versus* non-dippers. So, the putative link between GM-derived metabolites and BP dipping status remains unknown.

Methods

We investigated a cohort of male volunteers who were prospectively recruited and subjected to 24h-ABPM, stool sample collection and a medical questionnaire. A patient was categorised as non-dipper if the ratio between night and day systolic BP was >0.9. The patients were categorised in two groups, i.e. NT or HT, on the basis of the European Society of Hypertension criteria (https://www.eshonline.org). NT was defined by

Table 1. Clinical characteristics of the cohort (dippers vs non-dippers).

	Dippers	Non-dippers	p Value
N	31	13	
Age (years)	50.6 ± 9.9	53 ± 10.4	0.95
BMI (kg/m^2)	26 ± 3.4	26.9 ± 3.8	0.39
Smokers (%, N)	16.1 % (5)	7.7 % (1)	0.46
Alcohol (glass/week)	4.9 ± 5	4.1 ± 4.3	0.78
Family HT (%, N)	42 % (13)	53.8 % (7)	0.47
Diabetes (%, N)	3.2 % (1)	0	ns
CV history (%, N)	19.3 % (6)	30.7 % (4)	0.41
GE history (%, N)	42 % (13)	46.1 % (6)	0.8
24h Systolic BP (mmHg)	131.6 ± 12.1	132.9 ± 18.7	0.96
24h Diastolic BP (mmHg)	81.5 ± 9.5	81.5 ± 13.4	0.74
24h Mean BP (mmHg)	97.6 ± 10.2	98.9 ± 13.6	0.89
Night/Day Systolic BP ratio	0.84 ± 0.04	0.96 ± 0.04	<0.0001
Anti-HT treatment (%, N)	38.8 % (12)	53.7 % (7)	0.35

BMI: body mass index; BP: blood pressure; CV: cardiovascular; GE: gastro-enterological; HT: hypertension; ns: not significant.

Table 2. Blood pressure values between patients with anti-hypertensive medications (treated) and without anti-hypertensive medications (untreated).

	Treated	Untreated	p Value
N	19	25	
24h Systolic BP (mmHg)	134.5 ± 15.8	130.1 ± 12.8	0.37
24h Diastolic BP (mmHg)	81.8 ± 11.6	81.3 ± 10.1	0.99
24h Mean BP (mmHg)	99.5 ± 11.8	96.9 ± 10.8	0.44
Daytime Systolic BP (mmHg)	140.3 ± 16.1	136 ± 13.8	0.43
Daytime Diastolic BP (mmHg)	86.5 ± 11.9	86.8 ± 11.1	0.95
Daytime Mean BP (mmHg)	104.3 ± 12.2	101.8 ± 12.4	0.51
Night-time Systolic BP (mmHg)	123.4 ± 17.6	118.1 ± 12.5	0.37
Night-time Diastolic BP (mmHg)	72.9 ± 11.9	70.8 ± 10.5	0.72
Night-time Mean BP (mmHg)	90.3 ± 13.1	85 ± 12.4	0.21

BP: blood pressure.

mean 24h BP levels <130/80 mmHg in untreated individuals with or without isolated nocturnal HT (≥120 mmHg (systolic) and/or ≥70 mmHg (diastolic)) but without isolated daytime HT (≥135 mmHg (systolic) and/or ≥85 mmHg (diastolic)). HT was defined by mean 24h BP levels ≥130 mmHg (systolic) and/or ≥80 mmHg (diastolic) or by isolated daytime HT (≥135 mmHg (systolic) and/or ≥85 mmHg (diastolic)) or in case of use of antihypertensive medications whatever the BP levels. A subgroup analysis was performed between the patients with *versus* without anti-hypertensive medications. Metabolomics analyses were conducted on stool supernatants using Nuclear Magnetic Resonance (NMR) and the CPMG relaxation-editing sequence with presaturation, as previously detailed [2]. Faecal concentrations of acetate, butyrate and propionate were obtained by integrating the signals at 1.93 ppm, 1.56 ppm and 1.05 ppm, respectively. Univariate metabolomics data were subjected to a Mann–Whitney test. Mann–Whitney test and Chi-square test were used to compare continuous and categorical clinical variables, respectively.

Results

Our 44-case cohort included 13 non-dippers (29.6%) and 31 dippers, with 35 HT (79.4%) and 9 NT patients. Ten non-dippers (28.6%) and 25 dippers were HT. Nineteen HT patients were under anti-hypertensive medications (43.1%), including 7 non-dippers and 12 dippers. The mean age and body mass index (BMI) of the cohort were 50.8 ± 9.5 years and 26.3 ± 3.5 kg/m^2, respectively. No significant difference in BP values, age, BMI, smoking habits, alcohol consumption, familial HT, personal history of diabetes, cardiovascular or gastro-intestinal disorders was observed between

dippers and non-dippers (Table 1). The comparison of BP levels between patients with anti-hypertensive medications (i.e. 'treated') and those without any anti-hypertensive treatment (i.e. 'untreated') did not show any significant differences (Table 2). The relative quantification of faecal SCFAs showed higher amounts of acetate, butyrate and propionate in the stools of non-dippers (n = 12) *versus* dippers (n = 26) (p = 0.0252, p = 0.0468, and p = 0.0496, respectively; n = 38 *in toto*) (Figure 1(A)). Multivariate statistical analyses by the means of PCA-X model of reduced and normalised spectral data lead to the exclusion of 5 dippers and 1 non-dipper because of uninterpretable data. The faecal amounts of acetate, butyrate and propionate were higher in non-dippers (n = 5) *versus* dippers (n = 16) in patients without anti-hypertensive medications (p = 0.0414, p = 0.0108, and p = 0.0602, respectively; n = 21 *in toto*) (Figure 1(B)). When focussing only on HT patients without any anti-hypertensive medications, a not significant trend for higher amounts of the 3 main SCFAs was still found in the stools of non-dippers (n = 2) *versus* dippers (n = 12) (p = 0.0556; n = 14 *in toto*).

Discussion

To the best of our knowledge, the BP dipping status has never been associated with GM composition or its derived metabolites. The non-dipping BP pattern reflects a disruption in the circadian BP rhythm [4,5]. Several molecular components of the circadian timing system controlled by the central and peripheral clocks have been involved in metabolic abnormalities leading to non-dipping BP profile [4]. This circadian misalignment between clocks is not well understood. However, it may implicate the GM [6,7]. Indeed, the relative abundance of 60% of the total gut bacteria and their metabolites undergo circadian variations, which may be disrupted in case of dysbiosis and/or circadian misalignment [6].
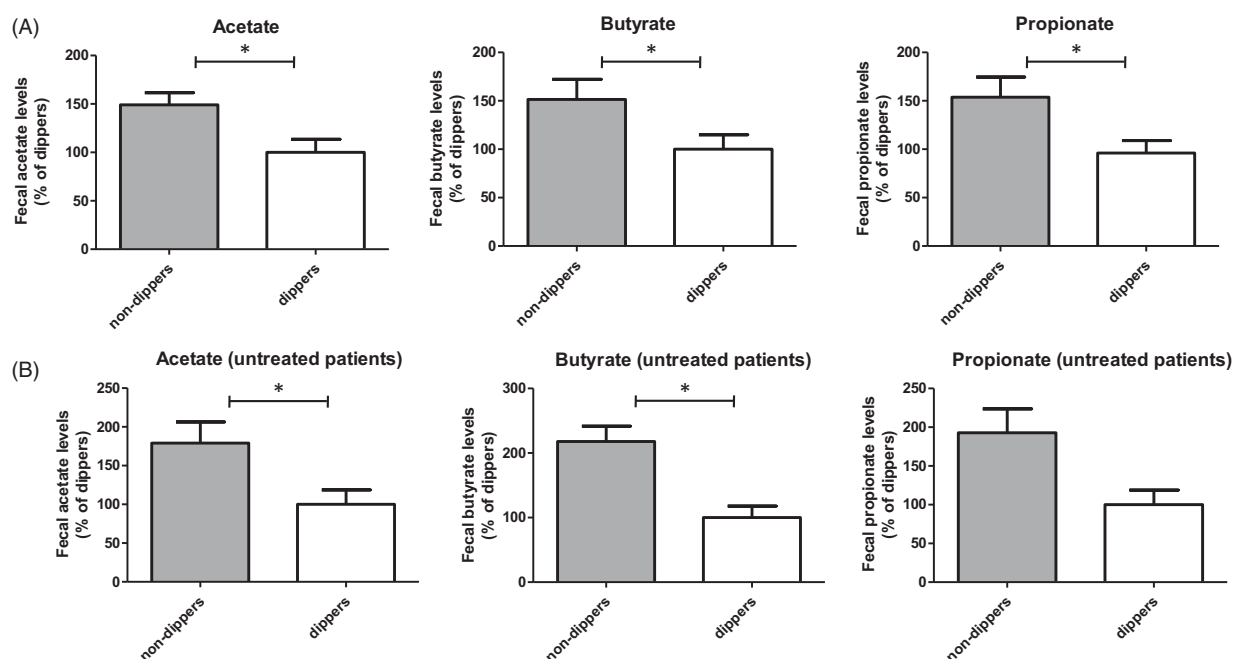
Figure 1. (A) Relative amounts of acetate, butyrate and propionate in the stools of non-dippers ($n = 12$) *versus* dippers ($n = 26$) in the whole cohort. *$p < 0.05$. (B) Relative amounts of acetate, butyrate and propionate in the stools of non-dippers ($n = 5$) *versus* dippers ($n = 16$) in the subgroup of patients without anti-hypertensive medications (untreated patients). *$p < 0.05$.

Moreover, the integrity of GM and its production of metabolites, including the SCFAs, seem essential for the circadian rhythmicity of gene expression in several organs [8,9]. In both mice and humans, Thaiss *et al.* showed that jetlag-induced dysbiosis promotes the development of obesity and glucose intolerance, which are transferrable to germ-free mice through faecal transplantation [10]. On the basis of these observations, one may speculate that disruption in the circadian BP rhythm (i.e. the non-dipping BP profile) may be associated with a disrupted rhythmicity of GM-mediated metabolite secretion, including SCFAs. None of our patients presented metabolic dysfunctions or confounding factors, when comparing dippers *versus* non-dippers. Although confirmatory data in larger cohorts are obviously needed, our observation of a putative link between GM and stool metabolome and BP dipping may unravel innovative pathophysiological investigations in the field.

Disclosure statement

All the authors declare that they have no conflict of interest involving the work under consideration for publication.

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