



Sympathoinhibition to Bezold–Jarisch reflex is attenuated in protein malnourished rats

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ABSTRACT

Malnutrition affects cardiovascular reflexes, including chemoreflex and baroreflex. In this study we assessed the hypothesis that malnourishment changes the responses in mean arterial pressure (MAP), heart rate (HR) and renal sympathetic nerve activity (RSNA) evoked from Bezold–Jarisch reflex (BJR). Fischer rats were fed diets containing either (6% malnourished or 14% control) protein for 35 days after weaning. There were no differences in baseline MAP (102 ± 4 vs. 95 ± 3 mmHg) whereas higher baseline HR (478 ± 18 vs. 360 ± 11 bpm; $P < 0.05$), and reduced sympathoinhibition (Δ RSNA = -54 ± 9 vs. $-84 \pm 7\%$; $P = 0.0208$) to BJR activation were found in malnourished rats. We conclude that malnutrition affects the sympathetic control of BJR.

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Protein malnutrition is a worldwide affection (Food And Agriculture Organization of the United Nations, 2008 [26]) that changes physiological and long-term metabolism [2,24,30], provoking consequences associated to diseases [20,21,25]. Deficiencies in dietary intake also modifies the cardiovascular homeostasis [14,18], likely evident on renal hemodynamics and on the cardiovascular reflexes [1,3,4,19,27,30].

Cardiopulmonary or Bezold–Jarisch reflex (BJR) is important for short term regulation of the blood pressure [22,36,38]. The effects evoked from cardiopulmonary chemoreceptors include hypotension, bradycardia and apnea [34]. The mechanisms involved in these aforementioned responses depend not only on sympathoinhibition, but also on a vagally mediated bradycardia [8].

BJR share pathways with baroreflex circuitry [9,36,41]. BJR activation decreases vasomotor outflow [15,17], mostly revealed following denervation of baroreceptors, which reinforce its role in the hemodynamic control [7].

Previous reports support the hypothesis of autonomic impairment during malnutrition, as elicited by changes in baroreflex gain

[19] and increases in the chemoreflex responsiveness [29]. In this study, we compared both cardiovascular and sympathetic reactivity to BJR activation between malnourished and control rats.

All the experimental procedures were conducted in accordance with the guidelines established by Brazilian Council for Animal Experimentation and our local Committee (CEUA Protocol # 2009/12). Male Fischer rats were used in this study. The animals were kept in individual cages and fed with both regular or low-protein diet and water *ad libitum*, in a climate controlled area (24°C) on a 12-h dark-light cycle.

We used an established model of protein malnutrition [19,27,29,35]. During pregnancy and weaning periods, females received regular rat chow and filtered water *ad libitum*. The offspring were randomly picked up and eight puppies were kept per mother, and the weaning period was set to 28 days. After the weaning, male rats were separated from their mothers and kept in individual cages. During next 35 days, rats were fed with either normal or low protein content diet, to obtain our two experimental groups: control and malnourished, respectively. The regular protein diet contained 14% protein while the low-protein diet contained 6% protein. The diets were isocaloric (422 kcal/100 g of diet) and the salts and vitamins were also similar in both diets. Animals were kept under these diet protocols for 35 days and were used for experiments in the subsequent day (36th).

We compared the responses in renal sympathetic nerve activity (RSNA), mean arterial pressure (MAP) and heart rate (HR) evoked by BJR activation between malnourished rats ($n = 6$) and control

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Table 1
Baseline values of body weight, mean arterial pressure (MAP), heart rate (HR) and changes in renal sympathetic nerve activity (RSNA), MAP and HR evoked by Bezold–Jarisch reflex activation in control and protein malnourished rats ($n=6$ each).

	Baseline values			Responses to BJR activation			
	Body weight (g)	MAP (mmHg)	HR (bpm)	Δ RSNA (%)	Δ MAP (mmHg)	Δ HR (bpm)	Δ HR (%)
Control	197 \pm 3	95 \pm 3	360 \pm 11	-54 \pm 9	-29 \pm 5	-223 \pm 27	-54 \pm 12
Malnourished	77 \pm 3*	102 \pm 4	478 \pm 18*	-84 \pm 7*	-24 \pm 4	-222 \pm 47	-49 \pm 12
<i>P</i> value	0.0001	0.07	0.0001	0.0208	0.4712	0.9724	0.4045

* $P < 0.05$ vs. control.

($n=6$) rats. The agonist of 5-HT₃ receptors Phenylbiguanide (PBG) at dose of 5.0 μ g/kg was used to stimulate BJR according to previously described [33]. Technical procedures used to record RSNA were as previously described [40]. Under urethane (Sigma, USA) anesthesia (1.2–1.4 g/kg i.p.), a tracheotomy was done to maintain airways opened. The adequacy of anesthesia was verified by the absence of a withdrawal response to nociceptive stimulation of a hindpaw. Supplemental doses of urethane (0.1 g/kg i.v.) were given when necessary. Body temperature was kept in the range of 36.5–37.0 °C with a thermo pad and a heating lamp. Catheters were placed into femoral artery and vein (to record cardiovascular parameters and drugs injection, respectively). From blood pressure (BP), MAP and HR were calculated on line. The left renal nerve was isolated, covered with mineral oil and put in contact with a silver bipolar electrode. RSNA signal was amplified by 10 K, filtered (100–1000 Hz), displayed on an oscilloscope and monitored by means of an audio amplifier. The filtered nerve activity signal was rectified; integrated (resetting every second), displayed online and acquired with BP using Powerlab 4/20–LabChart 7.1 (ADInstruments, Sydney, Australia). All RSNA data were digitized at 1 kHz. The noise level of the RSNA recording system was determined post-mortem and subtracted from initial RSNA values.

All the surgical procedures were performed in approximately 30 min. After a stabilization period of 30 min, an intravenous injection of PBG (5.0 μ g/kg) was performed to activate BJR. The volume of each intravenous injection was not greater 0.1 mL/100 g of body weight. Following, it was waited an additional period of 10 min or until the values returned to the baseline. At the end of experiments, rats were euthanized by an overdose of anesthetic.

RSNA analysis—baseline values sampled 5 min before the first PBG injection were taken as 100% and the changes evoked by BJR activation were considered as the variation of the above-mentioned percentage. **Data analysis**—body weight, RSNA, MAP and HR data were compared between control and malnourished groups by using unpaired Student *t*-test. Significance was taken at $P < 0.05$. Data are presented as means \pm SEM.

After 35 days of protein restriction, we observed that the body weight in malnourished rats was markedly lower than the control group (77 \pm 3 vs. 197 \pm 3 g; $P < 0.001$; respectively). Malnourished group showed significantly higher baseline HR compared to that found in control (HR: 478 \pm 18 vs. 360 \pm 11 bpm; respectively; $P < 0.05$). However, there were no differences in baseline MAP values found in both control and malnourished groups (MAP: 94 \pm 3 vs. 102 \pm 4 mmHg). Table 1 shows MAP and HR baseline values and body weight in control and malnourished rats.

Immediately following intravenous bolus injections of PBG (5.0 μ g/kg), control and malnourished rats presented reductions in both MAP (Δ MAP: -29 \pm 5 vs. -24 \pm 4 mmHg; respectively) and HR (Δ HR: -223 \pm 27 vs. -222 \pm 47 bpm; respectively), but no differences were found in the range of these absolute values. When calculating HR changes as percentage, it is clearly shown that it is not attenuated, as malnourished and control rats showed equipotent bradycardic ranges (Δ HR: -49 \pm 12 vs. -54 \pm 12%; respectively; $P = 0.4047$). Also, we observed rapid and transient falls in RSNA (Fig. 1, panels A and B). Strikingly, however, the renal

sympathoinhibition was substantially attenuated in malnourished compared to control rats (Δ RSNA: -54 \pm 9 vs. -84 \pm 7%; respectively; $P = 0.0208$) (Fig. 1, panel C).

Protein malnutrition may cause diseases, consequence of a set of “programming” in which a stimulus or insult at critical or sensitive period early in life results in physiological and long-term metabolic changes [2,20,21,24,30]. The body weight of our malnourished animals was significantly smaller than the control group. Present data are in agreement with previous reports, confirming the development of malnutrition status and validating this animal model [4,16,20,23,27,29]. Several clinical and experimental evidences indicate that protein malnutrition changes the homeostasis [14,23,25,27,32], highlighting the necessity to better understand the impact of malnutrition in the cardiovascular control.

We found that baseline heart rate in malnourished rats was significantly higher compared to control animals, but no differences in MAP values were found. A previous study reinforced the idea that protein malnutrition changes the autonomic control, increasing cardiac sympathetic outflow and decreasing cardiac parasympathetic tone [18]. It was also shown changes in the control of other reflexes [19,29,35] such as increases HR and MAP variability in this protein restriction model [27]. Present findings thus confirm this cardiac autonomic imbalance in malnourished rats.

It has been suggested that the reflex control of BP probably involves both baroreflex and BJR [41]. The removal of baroreceptors increases the responsiveness to BJR [7,9], meaning that part of the responses to BJR in healthy models might be suppressed by baroreflex. However, impairment the baroreflex sensitivity and changes in both baroreflex and BJR have been reported in our experimental model [19,35]. Current data presents lower sympathoinhibition to BJR activation. Despite not having an exact explanation that might help us understand these findings, we raise plausible hypotheses. Malnourishment may cause morphophysiological changes in the whole body. It may include the 5-HT₃ peripheral receptors and their sensory function, as it has been demonstrated that malnutrition modifies serotonergic metabolism [6,31]. However, this seems unlikely, since we found equipotent HR and BP falls following BJR activation in the control and malnourished rats. Specifically concerning the key role of central organization of BJR and other reflexes, we speculate that malnutrition may also damage centrally mediated functions. It is supported by evidences showing that malnutrition during development can determine structural changes in the central nervous system [30].

It cannot be neglected that other autonomic components may modulate sympathetic reactivity to BJR [12,37]. Studies demonstrated that BJR differentially modulates sympathetic outflow to different organs. Two distinct stimuli affect the sympathetic outflow to lumbar and renal nerves in non-uniform magnitudes [37]. In this regard, chemical and mechanical stimuli to activate BJR also reduced renal and adrenal sympathetic activities in a diverse range [13]. Furthermore, peripheral and central integration with others sensory mechanisms may also subscribe this attenuated sympathetic reactivity found in this model of malnourishment. Once the level of activity innervating different target organs can be non-uniformly changed, thus leading to different patterns according

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