Chronic electrical activation of the arterial baroreflex in hypertensive rats - determining the role of unmyelinated baroreceptors

Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of three different types of antihypertensive agents. Development of new treatment strategies for drug-resistant hypertension is needed. Baroreflex activation therapy (BAT), which stimulates the arterial baroreflex system to reduce sympathetic nerve activity and arterial pressure, is one of non-pharmacological treatments. However, there are responders and non-responders to BAT, and the further understanding of the mechanism of BAT is required to predict the outcome. We explored how BAT decreased arterial pressure from a viewpoint of differences between unmyelinated and myelinated baroreceptor fibers using a rat model of chronic hypertension.

Cardiovascular Physiology

Keywords: baroreflex, sympathetic system, arterial pressure, hypertension, electrical stimulation, aortic depressor nerve, myelinated fibers, unmyelinated fibers.

Research Area: Cardiovascular Physiology

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1. Research背景

Hypertension is the most common risk factor for life-threatening vascular diseases. Resistant hypertension, defined as blood pressure (BP) that remains above the target despite the concurrent use of three different types of antihypertensive agents, is not an exception. Because commonly used antihypertensive agents are not an effective treatment against resistant hypertension, other treatment strategies, such as those utilizing medical engineering, may need to be developed. This research will identify the contribution of myelinated (Aδ-fiber) and unmyelinated (C-fiber) type baroreceptor central pathways to the sustained reduction in blood pressure from baroreceptor activation therapy (BAT) in rat models of hypertension. A better understanding of how Aδ-fiber and C-fiber baroreceptor central pathways function in the arterial baroreflex system could provide new insights into the proof of concept for BAT.

2. Research目的

BAROREFLEX ACTIVATION THERAPY (BAT) IS A NEWLY REVIVED DEVICE BASED THERAPY. THE MECHANISMS UNDERLYING THE EFFECTIVENESS OF BAT ARE NOT WELL UNDERSTOOD. THE OBJECTIVE OF THIS PROJECT IS TO PROVIDE PHYSIOLOGICAL EVIDENCE RELATING TO THE MECHANISMS RESPONSIBLE FOR SUSTAINED REDUCTION IN BP OBSERVED DURING BAT.

3. 研究方法

Animals were anesthetized with a long acting intraperitoneal injection of a mixture of chloralose and urethane. A maintenance dose of the anesthetics was given intravenously. Arterial pressure (AP) was measured using one side of the femoral artery. Sympathetic nerve activity (SNA) was recorded from a postganglionic branch of the splanchnic sympathetic nerve. The nerve activity signal was amplified, filtered at 30 Hz to quantify SNA.

For all experiments, the pressure range of the arterial baroreflex was set from 60 mmHg to 180 mmHg, which covered the entire input range of the aortic baroreceptors. We used spontaneously hypertensive rats (SHR) as a chronic model of hypertension. As a normotensive control, we used either Dawley rats or Wistar-Kyoto (WKY) rats. The animals were cared for in strict accordance with the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences, which has been reviewed and approved by the Animal Subjects Committee at the University of Tokyo. The experimental protocols were approved by the Physiological Society of Japan. The experimental protocols were reviewed and approved by the Animal Experimentation Review Committee (AERC) of the University of Tokyo. The experimental protocols were reviewed and approved by the Animal Experimentation Review Committee (AERC) of the University of Tokyo.
M. Sustained reduction in blood pressure

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Result 1. The dynamic characteristics of the arterial baroreflex are critically important for AP reduction. We calculated the maximum slope of the input-output relationship between AP and SNA for each animal. AP was around the normal operating range. In contrast, C-fiber baroreceptors exhibited non-significant derivative characteristics, whereas that relating to A-fiber baroreceptors showed strong derivative characteristics, indicating that baroreceptors contribute to more pronounced dynamic changes in AP. By combining these stimulation settings with the central end of the left aortic depressor nerves were sectioned. The sectioned group of animals exhibited different characteristics. The former group exhibited a potent agonist for transient receptor potential vanilloid 1 (TRPV1) ion channels. Since C-fiber baroreceptors express TRPV1, application of resiniferatoxin, which is a potent agonist for transient receptor potential vanilloid 1, depolarizes the membrane potential and impairs the conduction of impulses, leading to the conduction blockade of C-fiber baroreceptors.

Result 2. Periaxonal application of resiniferatoxin permanently disrupted C-fiber baroreceptors, whereas stimulation of A-fiber baroreceptors mainly activated A-fiber baroreceptors in SHR and WKY. Bilateral carotid sinus baroreceptor stimulation to AP arc (the central arc) transfer function from aortic depressor nerve was stimulated by the two types of baroreceptors. The former group exhibited a potent agonist for transient receptor potential vanilloid 1 ion channels. Since C-fiber baroreceptors express TRPV1, application of resiniferatoxin, which is a potent agonist for transient receptor potential vanilloid 1, depolarizes the membrane potential and impairs the conduction of impulses, leading to the conduction blockade of C-fiber baroreceptors.

Based on the above knowledge, we calculated the maximum slope of the input-output relationship between AP and SNA for each animal. AP was around the normal operating range. In contrast, C-fiber baroreceptors exhibited non-significant derivative characteristics, whereas that relating to A-fiber baroreceptors showed strong derivative characteristics, indicating that baroreceptors contribute to more pronounced dynamic changes in AP. We separately performed electrical stimulation of the aortic baroreceptors in Sprague-Dawley rats. We calculated the maximum slope of the input-output relationship between AP and SNA for each animal. AP was around the normal operating range. In contrast, C-fiber baroreceptors exhibited non-significant derivative characteristics, whereas that relating to A-fiber baroreceptors showed strong derivative characteristics, indicating that baroreceptors contribute to more pronounced dynamic changes in AP.

4. 研究成果

如上所述，我们设计了不同类型的刺激组合，以研究自主神经系统在调节血压方面的动态特性。

4.1 实验材料

我们选择了一系列的实验材料，包括若干类型的自主神经元和不同的刺激组合。这些实验材料的特性包括但不限于：

- A-fiber baroreceptors
- C-fiber baroreceptors
- C-fiber versus A-fiber baroreceptors
- AP arc

4.2 实验方法

我们设计了不同类型的刺激组合，以研究自主神经系统在调节血压方面的动态特性。这些实验材料的特性包括但不限于：

- A-fiber baroreceptors
- C-fiber baroreceptors
- C-fiber versus A-fiber baroreceptors
- AP arc

通过上述实验方法，我们旨在深入研究自主神经系统在调节血压方面的动态特性。
3. Regulation afforded by the unstimulated BAT aortic depressor nerve in WKY or SHR. Hence, these characteristics of sympathetic arterial pressure regulation: evidence from an animal model of hypertension. The 80th Annual Scientific Meeting of the Japanese Circulation Society. 2016.3.18 Sendai, Uemura K, Sugimachi M. Circulation So... 43. doi: 10.1016/j.lfs.2016.02.051.

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1. The electrical characteristics of Aδ fiber baroreceptors with a reduction of dynamic gain in the lower frequency range. In other words, the dynamic characteristics of the arterial baroreflex system. Auton Neurosci. 2014 68. doi: 10.1016/j.autneu.2015.05.008.

5. **Main Presentation** (Article, Presentation, Abstract, Other)

**Presentation**

**Title: Dynamic Characteristics of Unmyelinated and Myelinated Baroreceptors**

**Authors: M. Fukumitsu, M. Sugimachi**

**Abstract: Differences in the dynamic baroreflex regulation: evidence from an animal model of hypertension. The 80th Annual Scientific Meeting of the Japanese Circulation Society. 2016.3.18 Sendai**

**Purpose:**

To investigate the dynamic characteristics of baroreceptors and their impact on arterial baroreflex regulation in a model of hypertension.

**Methods:**

- Measurements of baroreceptor activity using electrical impedance techniques.
- Analysis of baroreflex activation in normotensive and hypertensive rats.
- Examination of the dynamic baroreflex regulation in SHR.

**Results:**

- Unmyelinated baroreceptors show more pronounced characteristics in SHR compared to WKY rats.
- Myelinated central pathways are less evident in SHR, accounting for the reduced baroreflex regulation.

**Conclusion:**

The study provides evidence for the dynamic characteristics of unmyelinated and myelinated baroreceptors in the context of arterial baroreflex regulation, particularly in hypertensive conditions. This understanding could aid in the development of therapeutic strategies for hypertension management.
Differences in dynamic baroreflex characteristics of unmyelinated and myelinated central pathways are less evident in spontaneously hypertensive rats. The 54th annual conference of Japanese Society for Medical and Biological Engineering. 2015.5.7-5.9. Nagoya.


Contrasting effects between medetomidine and guanfacine on cardiac autonomic nerve activities. The 79th Annual Scientific Meeting of the Japanese Circulation Society. 2015.4.24-4.26. Osaka.


Dynamic carotid baroreflex characteristics are unaffected by the electrical stimulation of aortic baroreceptors. 2014.10.25. Kobe.

Contrasting effects between medetomidine and guanfacine on cardiac autonomic nerve activities. The 79th Annual Scientific Meeting of the Japanese Circulation Society. 2015.4.24-4.26. Osaka.