学 位 論 文 内 容 の 要 旨

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学 位 論 文 題 名

Precise Control of Heart Rate via Closed-Loop Medulla Stimulation and Non-Invasive Cardiac Modulation using Sonogenetics
（閉ループ延髄刺激による心拍数の精密制御と超音波による心機能制御）

Cardiovascular diseases are the main cause of global mortality, with autonomic nervous system (ANS) dysregulation as a critical pathophysiology. Traditional pharmaceutical and neuromodulation treatments like vagus nerve stimulation (VNS) face the limitations due to their invasive methos, lack of time-target, and inability to precisely modulate sympathetic-parasympathetic balance. This research investigated the ability of medulla for precise autonomic neuromodulation using heart rate as the index and established a non-invasive method to control medullary sympathetic output.

The systematic investigation of open-loop electrical stimulation in anesthetized Wistar rats (n=24) quantified parameter-response relationships across three targets: rostral ventrolateral medulla (RVLM), caudal ventrolateral medulla (CVLM), and cervical vagus nerve. RVLM stimulation evoked immediate tachycardia with concomitant PR interval shortening while CVLM stimulation induced profound bradycardia without conduction effects. Crucially, I demonstrated frequency dependence as a fundamental factor in electrical stimulation. VNS produced expected bradycardia but with significant PR prolongation. Heart rate variability (HRV) analysis (SDRR, SD1, SD2) confirmed sustained heart rate changes during effective stimulation. Building on parametric characterization, I engineered a real-time closed-loop method implementing a bang-bang control algorithm to maintain HR at specific targets (+20% or -10% of baseline) via RVLM, CVLM, or VNS stimulation in rats. All three sites achieved high-precision control (Control Degree: RVLM 98.02%, CVLM 98.11%, VNS 98.49%) and minimal fluctuation. Non-invasive sonogenetics employed virus vectors to express mechanosensitive ion channel TRPC6. Significant tachycardia was evoked specifically at a pulse repetition frequency (PRF) of 800 Hz and high pressure (1.24 MPa, achieved with 600 mVpp input). No response occurred at lower pressure (0.63 MPa) or PRFs (20-400 Hz), or in control group expressing tdTomato, or in the non-injected hemisphere.

Electrical stimulation of the RVLM and CVLM provides precise, rapid, and effective bidirectional control of the heart rate with closed-loop method. The non-invasive sonogenetics approach opens novel pathways for clinical neuromodulation without implants. This work provides the foundation for next-generation neuromodulation therapy of cardiovascular diseases.