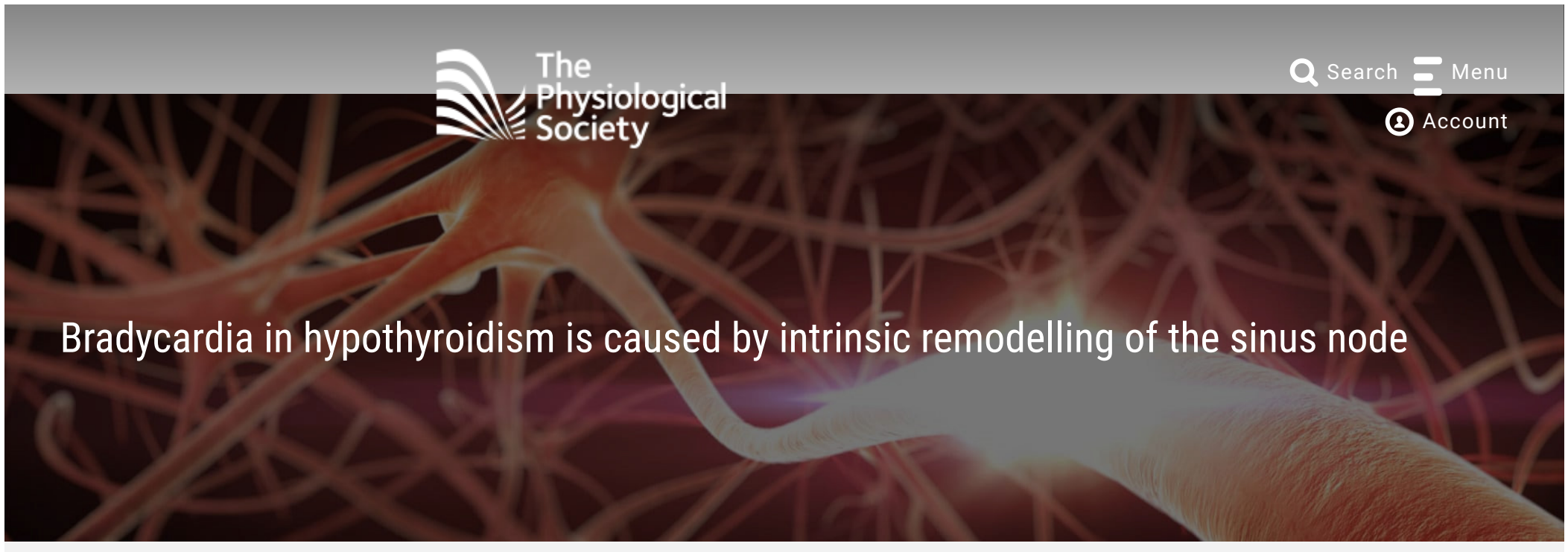


Bradycardia in hypothyroidism is caused by intrinsic remodelling of the sinus node

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Poster Communications: Bradycardia in hypothyroidism is caused by intrinsic remodelling of the sinus node

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Bradycardia (slow heart rate) is a characteristic cardiac phenotype seen in clinical hypothyroidism. The mechanism underlying the bradycardia is unknown. Potential causes include altered autonomic nerve activity and/or intrinsic remodelling of the sinus node. We have characterised the hypothyroid (HT) sinus node and identified the important mechanisms responsible for the bradycardia. Sprague Dawley rats (male, 260-350 g, n=18) were made HT with 6-n-propyl-2-thio-uracil (10 mg/kg/day for 15 days). Control cohort (n=20) received vehicle only. ECGs were recorded in anesthetised animals (ketamine, 100 mg/kg) under control conditions and after complete autonomic block with propranolol (2 mg/kg) and atropine (1 mg/kg). Animals were sacrificed by cervical dislocation, hearts extracted and Langendorff perfused with Tyrode's solution at 37°C and intrinsic heart rate measured. In sinus node, atrial and ventricular tissue biopsies mRNA abundance was measured using qPCR. Data are presented as mean±SEM and one-way ANOVA was used for statistical comparison. Animal work was approved by Marmara University animal experiments ethical committee. HT animals showed a reduced heart to body weight ratio (3.9±0.2 vs. 4.7±0.1 mg/kg in control, P<0.05) and developed severe bradycardia (253±15 vs. 428±6 beats per minute, bpm, in control animals, P<0.05). After complete autonomic block the intrinsic heart rate recorded in vivo was 223±9 bpm in HT and 404±19 bpm in control animals. In vitro, in the Langendorff perfused heart, the intrinsic rate measured in HT and control hearts was 186±9 and 238±7 bpm (P<0.01), respectively. Inherent automaticity in the sinus node is due to the voltage- and Ca2+-clock pacemaker mechanisms. In the HT sinus node, transcripts for key voltage-clock components were significantly downregulated: funny current (If; HCN4 down by 79%, P<0.05), L-type Ca2+ current (ICa,L; Cav1.2 down by 66%, P<0.05) and T-type Ca2+ current (ICa,T; Cav3.1 down by 77%, P<0.05). Similar downregulation was observed in Ca2+-clock components: sarcoplasmic reticulum Ca2+ ATPase (SERCA2a, down by 90%, P<0.01) and ryanodine receptor (RyR2, down by 77%, P<0.05). The plasma membrane Ca2+ ATPase (PMCA1) responsible for Ca2+ extrusion out of the cell was downregulated by 85% (P<0.05) in the HT sinus node. Consistent with these findings, we identified potential thyroid hormone response elements in the 10 kb promoter region of HCN4 using in-silico analysis; it is already known that thyroid hormone binds to thyroid hormone response elements in the promoter region of SERCA2a and regulates its expression.(1) In the HT sinus node, downregulation of HCN4, Cav1.2 and Cav3.1 coupled with significant loss of SERCA2a and RyR2 is likely to compromise the voltage- and Ca2+-clock pacemaker mechanisms. Thus, ion channel remodelling intrinsic to the sinus node is the likely cause of bradycardia in hypothyroidism.

Where applicable, experiments conform with Society ethical requirements.

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