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Lipopolysaccharide exacerbates loss-of-function of the sodium channels in human-induced stem cell-derived cardiomyocytes from patients with Brugada syndrome

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Backgrounds: Brugada syndrome (BrS) is a rare channelopathy with risk of lifethreatening tachyarrhythmias. Fever is a well-known trigger for the occurrence of arrhythmias in BrS and a hallmark of infection, suggesting a connection of inflammation and arrhythmogenesis of BrS. However, experimental studies regarding roles of inflammation for arrhythmogenesis of BrS and underlying mechanism are still lacking.
Objectives: The study aimed to investigate whether inflammation exacerbate lossof-function of sodium channels, a key phenotypic change in BrS, whether the influence of inflammation on BrS-phenotype is gene specific and which mechanism underlies the effects of inflammation on BrS.
Methods: Human induced stem cell derived cardiomyocytes (hiPSC-CMs) were generated from three healthy donors (D1, D2 and D3) and four BrS-patients, carrying a SCN5A-polymorphism (c.3148G>A), a SCN10A-variant (c.3749G>A), a SCN1B compound variant (c.629T>C and c.637C>A) and a CACNB2-varainat (c.428C>T), respectively. LPS was applied to challenge hiPSC-CMs to mimic inflammation in cells. After LPS treatment for 24h, patch-clamp measurements were carried out to assess changes in the sodium channel currents and gating kinetics.
Results: LPS treatment induced inflammatory responses including ROS productions in hiPSC-CMs. After LPS-treatment, sodium current density decreased significantly in SCN10A- and SCN5A-hiPSC-CMs, slightly in SCN1B-hiPSC-CMs, but not in CABN2- and donor-hiPSC-CMs. LPS also changed sodium channel gating kinetics including activation, inactivation and recovery from inactivation, in ways that are in agreement with the current changes. To investigate mechanisms underlying LPS-effects on sodium channels, NAC (N-acetyl-L-cysteine), a blocker of ROS (reactive oxygen species) production, was used to reveal the involvement of ROS in LPS-effect. NAC along didn't affect the sodium current, but prevented the LPS-induced reduction of sodium channel currents and changes in gating kinetics, suggesting a contribution of ROS to LPS-effects. Then, hydrogen peroxide (H2O2), a main form of ROS in cells, was used to mimic oxidative stress. H2O2 mimicked the LPS effects on sodium channel currents and gating kinetics, implying that ROS might mediate LPS-effects on sodium channels. H2O2 displayed no acute direct effect on sodium channel currents, but its effects could be attenuated by a PKC blocker Chelerythrine, indicating that PKC may play a role in modulating the sodium channels. Action potential measurements showed that the maximal depolarization velocity (Vmax) reduced after treatment of LPS in BrS but not in donor cells.
Taken together, LPS inhibited INa, which resulted from changes in channel gating kinetics and resulted in a reduction of Vmax of APs in BrS-cells but not in healthy cells. The effects of LPS were mediated by ROS and PKC and were also different in different BrS-cell lines.
Conclusions: LPS can exacerbate the loss-of-function of sodium channels and LPSeffect may be gene specific; Inflammation may play an important role in the pathogenesis of some BrS-patients; Anti-inflammation treatment may be helpful for preventing occurrence of arrhythmias in some BrS-patients.