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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Binge Alcohol Exposure Triggers Atrial Fibrillation Through T-Type Ca^{2+} Channel Upregulation via Protein Kinase C (PKC) / Glycogen Synthesis Kinase 3β (GSK3β) / Nuclear Factor of Activated T-Cells (NFAT) Signaling

— An Experimental Account of Holiday Heart Syndrome —

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Background: The association between binge alcohol ingestion and atrial fibrillation (AF), often termed "holiday heart syndrome", has long been recognized. However, the underlying cellular and molecular mechanisms are unknown.

Methods and Results: An experimental model of binge alcohol-induced AF was developed to elucidate the mechanisms linking acute ethanol exposure to changes in ion channel transcription and AF susceptibility. AF-susceptibility during transesophageal electrical stimulation was enhanced 8 h after, but not immediately or 24 h after, acute alcohol intake. T-type calcium channel (TCC) blockade and calcineurin inhibition diminished the AF-promoting effect of ethanol. Long-term (8–24 h) exposure to ethanol augmented TCC isoform-expression ($Ca_V3.1$ and $Ca_V3.2$) and currents in cardiomyocytes, accompanied by upregulation of the transcription factors, Csx/Nkx2.5 and nuclear factor of activated T-cells (NFAT), in the nucleus, and of phospho-glycogen synthesis kinase 3β (GSK3β) in the cytosol. Inhibition of protein kinase C (PKC) during the 7- to 8-h period following ethanol exposure attenuated susceptibility to AF, whereas acute exposure did not. GSK3β inhibition itself upregulated TCC expression and increased AF susceptibility.

Conclusions: The present study results suggest a crucial role for TCC upregulation in the AF substrate following binge alcohol-drinking, resulting from ethanol-induced PKC-activation that hyperphosphorylates GSK3β to cause enhanced calcineurin-NFAT-Csx/Nkx2.5 signaling. These observations elucidate for the first time the potential mechanisms underlying the clinically well-recognized, but mechanistically enigmatic, "holiday heart syndrome".

Key Words: Alcohol; Atrial fibrillation; Electrophysiology; Ion channels

Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia. Although certain risk factors, such as age, hypertension, serum metabolites and heart failure are well-established,[1–3] the causes and mechanisms remain unknown in many patients. There is conflicting evidence regarding an association between long-term alcohol consumption and the risk of AF.[4] In contrast, an association between binge alcohol-drinking and AF, often termed "holiday heart syndrome", has been widely recognized.[5] Holiday heart syndrome refers to cardiac arrhythmias, particularly AF, that occur after an alcoholic binge in individuals showing no other evidence of heart disease, which usually convert to normal sinus rhythm within 24 h.[6] Several potential mechanisms have been postulated by which an alcoholic binge could cause arrhythmias. Alcohol-induced increases in plasma-free fatty acids and catecholamines are thought to be arrhythmogenic,[7] as is the principal metabolite of alcohol, acetaldehyde.[8] However, the precise electrophysiological mechanisms that connect acute ethanol consumption to AF are largely unknown.

Editorial p 1909

Pulmonary veins (PVs) are important foci for initiation of paroxysmal AF and are also associated with AF maintenance.[9] PVs contain cardiomyocytes with electrical activ-

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