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Trafficking defects underlying the mechanisms of acquired Brugada syndrome induced by amitriptyline

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Brugada syndrome (BrS), a cardiac disorder predisposing to a high risk of sudden cardiac death, is associated with loss-of-function in sodium current (INa). Exposure of tricyclic antidepressants (TCAs) has been reported to induce BrS phenotype. However, the mechanisms by which TCAs induce BrS remains unclear. Therefore, we investigate the effect of TCAs on Nav1.5. Four widely used TCAs (amitriptyline, nortriptyline, clomipramine and desipramine) were tested for their pharmacological effect. Neonatal rat ventricular myocytes were used for patch clamp and immunofluorescence experiments. Nortriptyline, clomipramine and desipramine showed similar effect on I_{peak} of Nav1.5 by way of either acute administration or chronic incubation for 24h. While amitriptyline exhibit more impressive effect through chronic incubation than through acute administration. I_{peak} of Nav1.5 decreased for 43.4% after co-incubation with amitriptyline for 24h. No significant difference in steady-state activation and steady-state inactivation processes was observed between cells before and after co-incubation with amitriptyline. Confocal imaging showed decreased expression of Nav1.5 on plasma membrane and increased expression of Nav1.5 around nuclear in cells co-incubation with amitriptyline for 24 h, which indicated trafficking abnormalities of Nav1.5 induced by amitriptyline. We provide evidence that amitriptyline can induce the trafficking abnormalities of Nav1.5. The chronic effect of amitriptyline may lay foundation for researches on potential treatment of Nav1.5-associated BrS.

Biography

Xi Chen has completed her master degree study from PLA General Hospital, and is majoring in her doctoral study from PLA General Hospital. Her major research covers electrophysiological study related to arrhythmia and mitochondrial genetic study related to hypertension. She has published 3 papers as first author during her studies.

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