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Postnatal developmental changes in sensitivity of L-type Ca2+ channel to inhibition by verapamil

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<Background> L-type Ca2+ channel (ICa,L) blockers can be divided in three groups on the basis of their structures; namely, dihydropyridines, benzodiazepines and phenylalkylamines. They are widely used for the treatment of hypertension and tachyarrhythmias in clinical settings. However, intravenous administration of the phenylalkylamine verapamil for tachyarrhythmias is considered to be contraindicated in neonates and infants, due to the perceived risk of hypotension or bradycardia. However, its ionic basis has yet to be fully elucidated. In the present investigation, we examined the postnatal developmental changes in the sensitivity of ICa,L to the three classes of its blockers using mouse heart model.

<Methods> Ventricular myocytes were enzymatically digested from the heart of postnatal days 0, 7, 14, 21, 28 and adult (10-15 weeks) mice using similar Langendorff-perfusion methods. Whole-cell patch-clamp technique was used to record ICa,L in ventricular myocytes of various postnatal ages in the absence of presence of nifedipine, diltiazem and verapamil at concentrations of 1 nM to 1 μ M. Concentration-relationship was constructed by plotting the percentage inhibition of ICa,L as a function of drug concentrations.

<Results> There is a postnatal developmental increase in the amplitude of ICa,L. ICa,L in day-28 and adult ventricular myocytes are larger than that in day-0, day-7, day-14 and day-21 myocytes. The half-maximally inhibitory concentration (IC50) for the inhibition of ICa,L by verapamil was significantly smaller in day-0, day-7, day-14 and day-21, compared with day-28 and adult ventricular myocytes. In contrast, there were no significant differences in IC50 for the inhibitory action of nifedipine or diltizem in all postnatal developmental ages.

<Conclusions> ICa,L in neonates and infants exhibits a higher sensitivity to inhibition by verapamil compared with that in child and adult stages in the mouse model, which may explain at least partly severity of the verapamil-induced hypotension in neonates and infants.