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STEREOSPECIFIC MEMBRANE INTERACTIONS OF DRUG STEREOISOMERS AT CLINICALLY RELEVANT CONCENTRATIONS

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With respect to the mechanistic membrane interaction of drugs, there are two critical subjects: whether drug stereoisomers interact with membranes stereospecifically and whether they are effective in modifying membrane physicochemical properties at clinically relevant concentrations. We studied the comparative potencies of selected stereoisomers to interact with liposomal membranes at concentrations to exhibit beneficial and adverse action. Unilamellar vesicles were prepared with phospholipids and cholesterol to mimic the lipid compositions of cardiomyocyte and neuronal membranes. Stereoisomers of local anesthetic bupivacaine, β-adrenergic antagonist propranolol and anti-inflammatory ibuprofen were subjected at 5-200 μM to the reaction with biomimetic membranes and their membrane interactivities were determined by measuring fluorescence polarization. Bupivacaine stereoisomers interacted with 40 mol% cholesterol-containing cardiomyocyte-mimetic membranes to induce a significant increase in membrane fluidity at ~50 μM. Their membrane interactions showed the relative potency being R(+)-bupivacaine>rac-bupivacaine>S(-)-bupivacaine, which correlated to that of their cardiotoxicity. Such a stereostructure-dependent difference became greater with lowering drug concentrations. Bupivacaine is considered to localize at lipid-lipid and lipid-protein interfaces within cardiomyocyte membranes, affecting the lipid environment surrounding membrane-embedded sodium channels in a stereospecific manner. Both propranolol and ibuprofen stereoisomers also interacted at clinically relevant concentrations with neuro-mimetic membranes to change their fluidity with the relative potency being *R*(+)-propranolol>*rac*-propranolol>*S*( )-propranolol and being *S*(+)-ibuprofen>rac-ibuprofen>*R*( )-ibuprofen. The rank orders of membrane interactivity of all the tested drug stereoisomers agreed with those of their pharmacological and clinical effects. The opposite configuration allows molecules to interact with membrane chiral cholesterol enantioselectively and the specific β configuration of cholesterol's 3-hydroxyl group appears to be responsible for such selectivity. The stereospecific membrane interactivity has implications for medicinal chemistry as a methodological index for drug design to discriminate more active or toxic stereoisomers from less active or toxic ones.

Biography

H Tsuchiya received his PhD based on a clinical chemistry thesis from Gifu Pharmaceutical University. He served as a research investigator at National Center for Nervous, Mental and Muscular Disorders and University of Pennsylvania Monell Chemical Senses Center. He is presently a chief professor of Asahi University School of Dentistry. His current research interests are related to medicinal chemistry of anesthetics and phytochemicals. He has published more than 200 papers in international journals.

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