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Differentiation of Drug Stereoisomers by Their Stereostructure-Selective Membrane Interactions as One of Pharmacological Mechanisms

Authors : Maki Mizogami, Hironori Tsuchiya, Yoshiroh Hayabuchi, Kenji Shigemi

Abstract : Since drugs exhibit significant structure-dependent differences in activity and toxicity, their differentiation based on the mechanism of action should have implications for comparative drug efficacy and safety. We aimed to differentiate drug stereoisomers by their stereostructure-selective membrane interactions underlying pharmacological and toxicological effects. Biomimetic lipid bilayer membranes were prepared with phospholipids and sterols (either cholesterol or epicholesterol) to mimic the lipid compositions of neuronal and cardiomyocyte membranes and to provide these membranes with the chirality. The membrane preparations were treated with different classes of stereoisomers at clinically- and pharmacologically-relevant concentrations (25-200 μM), followed by measuring fluorescence polarization to determine the membrane interactivity of drugs to change the physicochemical property of membranes. All the tested drugs acted on lipid bilayers to increase or decrease the membrane fluidity. Drug stereoisomers could not be differentiated when interacting with the membranes consisting of phospholipids alone. However, they stereostructure-selectively interacted with neuro-mimetic and cardio-mimetic membranes containing 40 mol% cholesterol ((3β)-cholest-5-en-3-ol) to show the relative potencies being local anesthetic R(+)-bupivacaine > rac-bupivacaine > S(−)-bupivacaine, α2-adrenergic agonistic D-medetomidine > rac-medetomidine > L-medetomidine, β-adrenergic antagonistic R(+)-propranolol > rac-propranolol > S(–)-propranolol, NMDA receptor antagonistic S(+)-ketamine > rac-ketamine, analgesic monoterpenoid (+)-menthol > (−)-menthol, non-steroidal anti-inflammatory S(+)-ibuprofen > rac-ibuprofen > R(−)-ibuprofen, and bioactive flavonoid (+)-epicatechin > (−)-epicatechin. All of the order of membrane interactivity were correlated to those of beneficial and adverse effects of the tested stereoisomers. In contrast, the membranes prepared with epicholesterol ((3α)-chotest-5-en-3-ol), an epimeric form of cholesterol, reversed the rank order of membrane interactivity to be S(−)-enantiomeric > racemic > R(+)-enantiomeric bupivacaine, L-enantiomeric > racemic > D-enantiomeric medetomidine, S(–)-enantiomeric > racemic > R(+)-enantiomeric propranolol, racemic > S(+)-enantiomeric ketamine, (−)-enantiomeric > (+)-enantiomeric menthol, R(−)-enantiomeric > racemic > S(+)-enantiomeric ibuprofen, and (−)-enantiomeric > (+)-enantiomeric epicatechin. The opposite configuration allows drug molecules to interact with chiral sterol membranes enantiomer-selectively. From the comparative results, it is speculated that a 3β-hydroxyl group in cholesterol is responsible for the enantioselective interactions of drugs. In conclusion, the differentiation of drug stereoisomers by their stereostructure-selective membrane interactions would be useful for designing and predicting drugs with higher activity and/or lower toxicity.

Keywords : chiral membrane, differentiation, drug stereoisomer, enantioselective membrane interaction
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