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CysLT and EP receptors as targets for anti-seizure drugs: Preclinical data

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Accumulating circumstantial and experimental evidence support a role for arachidonic acid-derived inflammatory mediators in seizures. Accordingly, seizures induced by different chemoconvulsants are accompanied by time-dependent increase of leukotriene and prostaglandin synthesis. In addition, while 5-LOX and COX-2 inhibitors reduce, leukotrienes and prostaglandins, particularly PGE2, facilitate seizures, suggesting that these arachidonic acid metabolites play a role in seizure generation. Since seizure-related leukotriene and prostaglandin syntheses generate superoxide anion and selected antioxidants may decrease seizures, a number of studies have proposed that 5-LOX and COX-derived superoxide might play a major role in seizure generation and/or propagation. Moreover, since COX-2 is also involved in the metabolism of endocannabinoids, it has been suggested that COX-2 inhibition may decrease seizures by facilitating endocannabinoid-mediated inhibitory transmission. A definitive role for prostaglandins and leukotrienes, by themselves, in seizure facilitation was strengthened when it was shown that anti-PGE2 antibodies and CysLT1, EP1 and EP3 receptor antagonists decrease seizures. The reports that EP2 and DP1 receptor agonists decrease seizures constituted further evidence that the role of prostaglandin in seizure development is complex and that drug targeting shall consider the multiplicity of effects of a single prostaglandin, such as PGE2, but also the effects of the other metabolites of arachidonic acid, such as leukotrienes and PGD2. While current data suggests that EP1 and EP3 receptors may be interesting targets for novel anticonvulsants, the current availability and use of safe CysLT1 antagonists in the clinics may be a fast track for developing novel anti-seizure drugs, based on an anti-inflammatory rationale.

Biography

Carlos Fernando Mello has completed his MD at the age of 23 years and PhD at the age of 30 years, both from the Federal University of Rio Grande do Sul, and Postdoctoral studies from University of Kentucky. He is a full Professor of Medical Pharmacology at the Federal University of Santa Maria and has published more than a 130 papers in reputed journals and has been serving as an Editorial Board Member of Medicine.

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