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Voltage-gated sodium channel blockers as antimyotonic and antiarrhythmic agents

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Abstract

Voltage-gated sodium channel blockers are clinically used in several disorders of membrane excitability including cardiac arrhythmias, epileptic seizures, pain and myotonia. The safety of these drugs relies on their ability to block sodium channels in a frequency-dependent manner, allowing a selective inhibition of over excited cells while sparing the healthy organs. Among them mexiletine is an antiarrhythmic drug belonging to class IB. Besides its well-known antiarrhythmic activity, its usefulness in the treatment of skeletal muscle channelopathy, as myotonia, which are rare human genetic diseases, is now widely recognized. Mexiletine has been recently appointed as an orphan-drug in myotonic-syndromes. Nevertheless, it has been discontinued in many countries because of its side effects. Consequently, numerous attempts have been made in recent years to develop an alternative to mexiletine, including the design of new analogues that offer the same pharmacological effect but without the unwanted side effects. In the past decade, my research group has been focusing on the development of mexiletine and its relative, tocainide, analogues that helped to clarify the structural requirements for ameliorating the therapeutic profile, in terms of potency and use-dependent block of myofiber sodium currents. As these identified compounds were more potent channel blockers than the parent compounds, they have been proposed as mexiletine alternatives for the treatment of myotonia. Furthermore, compounds with a dual action as voltage-gated sodium channel blockers and anti-oxidants have been identified, that may have an interesting therapeutic action in degenerating myopathies in which the alteration of excitation-contraction coupling is accompanied by chronic inflammatory state and unbalanced oxidative stress. Some of these compounds showed also a better antiarrhythmic activity along with the same or less cardiovascular effects than mexiletine, thus presenting a higher selectivity of action and reduced side effects. Herein the results of this study will be presented.

Biography

Alessia Carocci currently works as a professor in University of Bari Aldo Moro, Italy

Publications

1. Novel insights in health-promoting properties of sweet cherries
2. The Effects of Cadmium Toxicity
3. Voltage Gated Sodium Channel Blockers: Synthesis of Mexiletine Analogues and Homologues
4. Effect of Methyl-β-Cyclodextrin on the antimicrobial activity of a new series of poorly water-soluble benzothiazoles
5. Nickel: Human Health and Environmental Toxicology
6. Effects of Sweet Cherry Polyphenols on Enhanced Osteoclastogenesis Associated With Childhood ObesityTable_1.doc
7. Effect of Methyl-β-Cyclodextrin on the antimicrobial activity of a new series of poorly water-soluble benzothiazoles
8. Finding solutions for agricultural wastes: Antioxidant and antitumor properties of pomegranate Akko peel extracts and β-glucan recovery†
9. Elucidation of the synergistic action of Mentha Piperita essential oil with common antimicrobials
10. Oxidative stress and neurodegeneration: the involvement of iron
11. A Focus on the Synthesis and Pharmacokinetics of Tocainide and its Analogues
12. Pyrroline Derivatives of Mexiletine-Like Compounds Have Dual Activity as Use-Dependent Sodium Channel Blockers and Antioxidant
13. Dual Action of Mexiletine and Its Pyrroline Derivatives as Skeletal Muscle Sodium Channel Blockers and Anti-oxidant Compounds: Toward Novel Therapeutic Potential
14. Response to Comment on Giuseppe Genchi et al. Mercury Exposure and Heart Diseases. Int. J. Environ. Res. Public Health 2017, 14, 74
15. A Mini-Review on Thalidomide: Chemistry, Mechanisms of Action, Therapeutic Potential and Anti-Angiogenic Properties in Multiple Myeloma

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