Mildronate: An Antiischemic Drug for Neurological Indications

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ABSTRACT

Mildronate (3-(2,2,2-trimethylhydrazinium)propionate; MET-88; meldonium, quaterine) is an antiischemic drug developed at the Latvian Institute of Organic Synthesis. Mildronate was designed to inhibit carnitine biosynthesis in order to prevent accumulation of cytotoxic intermediate products of fatty acid \(\beta\)-oxidation in ischemic tissues and to block this highly oxygen-consuming process. Mildronate is efficient in the treatment of heart ischemia and its consequences. Extensive evaluation of pharmacological activities of mildronate revealed its beneficial effect on cerebral circulation disorders and central nervous system (CNS) functions. The drug is used in neurological clinics for the treatment of brain circulation disorders. It appears to improve patients’ mood; they become more active, their motor dysfunction decreases, and asthenia, dizziness and nausea become less pronounced. Since the brain does not utilize fatty acids as fuel other mechanisms of action of mildronate in CNS should be considered. Several reports indicate the possible existence of an alternative, non-carnitine dependent mechanism of action of mildronate. Our recent findings suggest that CNS effects of mildronate could be mediated by stimulation of the nitric oxide production in the vascular endothelium by modification of the \(\gamma\)-butyrobetaine and its esters pools. It is hypothesized that mildronate may increase the formation of the \(\gamma\)-butyrobetaine esters. The latter are potent cholinomimetics and may activate eNOS via acetylcholine receptors or specific \(\gamma\)-butyrobetaine ester receptors. This article summarizes known pharmacological effects of mildronate, its pharmacokinetics, toxicology, as well as the proposed mechanisms of action.

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