TRANSPORT MECHANISM INVOLVED IN THE DISTRIBUTION OF CARNITINE AND ORGANIC CATIONS TO THE HEART

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Although various types of therapeutic agents have been known to exhibit unfavorable effects in hearts, little information is available on the molecular mechanism involved in drug distribution to the heart. We have previously demonstrated that carnitine/organic cation transporter OCTN2 (SLC22A5) transports not only carnitine but also organic cations (e.g. tetraethylammonium, quinidine and verapamil). The patients and model mice (jvs mice) of systemic carnitine deficiency, caused by mutation of OCTN2, exhibit cardiomyopathy, implying that OCTN2 plays some physiological role in the heart. In this study, we aimed to clarify the involvement of OCTN2 in the distribution of carnitine and organic cations to the heart. Immunohistochemistry demonstrated that OCTN2 was localized to the plasma membrane of the cardiomyocyte. Uptakes of [3H]carnitine and [3H]quinidine by mouse heart slices were remarkably decreased by addition of 0.5 mM unlabeled substrates, and at low temperature. The uptake of [3H]carnitine was Na⁺-dependent, and inhibited by carnitine analogs and several cationic compounds. Such inhibition profile was similar to that observed in HEK293 cells transfected with OCTN2. The uptake of [3H]carnitine by heart slices from jvs mice was significantly lower than that from wild-type mice, and was almost equal to that of [14C]mannitol. These results suggest that OCTN2 plays a major role in the uptake of carnitine by cardiomyocytes. In contrast, the uptake of [3H]quinidine was independent of Na⁺ and was not inhibited by carnitine analogs. In addition, the uptake of [3H]quinidine from jvs mice was almost equal to that from wild-type mice. RT-PCR analysis detected expression of mRNA for other cation transporters. Thus, involvement of transporters other than OCTN2 may account for the uptake of quinidine by the heart.