Modulation of MVA pathway during neuronal differentiation

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Mevalonate (MVA) pathway is involved in different cellular processes, leading to the production of both cholesterol and other compounds such as prenyls, Coenzyme Q, and Dolichol.Cholesterol is a very important lipid and its intracellular levels are regulated by the synthesis *via* the key enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) and by lipoprotein uptake *via* Low Density Lipoprotein receptor (LDLr). Several studies demonstrate a pivotal role of MVA pathway in different tissues but, little is known about its role in the brain. Here, the majority of cholesterol is present in oligodendrocytes and in neuronal membranes where this lipid plays structural and functional roles. Besides cholesterol, also other MVA pathway end-products play a significant roles in the brain. A working model for cholesterol homeostasis in the brain suggests that during embryogenesis, neurons are able to reach their cholesterol requirement by biosynthesis. Postnatally, neurons reduce or abandon their own synthesis up-taking it from astrocytes. Here, we investigate on modulation of the protein network involved in MVA pathway regulation and on the role of its end products during neuronal differentiation using as experimental model mouse neuroblastoma N1E-115 cells. Results highlight the involvement of this metabolic pathway during neurite outgrowth; in particular, the treatment with simvastatin, an inhibitor of HMGR, shows that the decreased activity of the enzyme is the cause rather than an effect of neuronal differentiation. Rescue experiments demonstrate a role for prenylated proteins rather than cholesterol in this physiological process. Thus, MVA pathway seems to play a key role in neuronal development.

Involvement of bradykinin and substance P in the lisinopril-induced upregulation of the cough reflex within the caudal nucleus tractus solitarii of the rabbit

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In previous studies we have shown that the cough reflex is potentiated by the angiotensin converting enzyme (ACE) inhibitor lisinopril, but not by the angiotensin II receptor blocker losartan in both anesthetized and awake rabbits. Since both lisinopril and losartan cross the blood-brain barrier, their central action at the level of the caudal nucleus tractus solitarii (NTS), the predominant site of termination of cough-related afferents, was investigated. Bilateral microinjections (30-50 nl) of losartan (5 mM), lisinopril (1 mM), bradykinin (0.05 mM), HOE-140 (0.2 mM, a bradykinin B_2 receptor antagonist), CP-99,994 (1 mM, a NK_1 receptor antagonist) were made into the caudal NTS of pentobarbital sodium-anesthetized, spontaneously breathing rabbits. Mechanical stimulation of the tracheobronchial tree and citric acid inhalation were used to induce cough reflex responses. Lisinopril, but not losartan consistently potentiated the cough reflex by increasing the number of coughs induced by each stimulation. This effect was reverted by HOE and CP-99,994. Cough potentiating effects were also induced by bradykinin. The results support the notion of a central action of lisinopril mediated by the same mechanisms that have been suggested to operate at the peripheral level, i.e., biochemical events including the accumulation of bradykinin and substance P.