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The development and characterization of novel ligands to ASICs

Acid sensing ion channels (ASICs) are a most important cellular sensor to extracellular media acidification. The tiny reduction of pH level can be converted into influx of sodium and calcium ions through these channels following the depolarization of cell membranes. In mammalians 4 genes coded structures of these ion channels but the principal importance has ASIC1a subtype widely distributed in brain and ASIC3 subtype expressed predominantly in peripheral neurons. ASICs are implicated in pain, neurological and psychiatric diseases but their therapeutic potential is limited by lack of selective ligands. We search ligands to ASICs in different herbal extracts, since medicinal plants can produce compounds to many cellular targets. As a result, one alkaloids' inhibitor of ASICs was purified from thyme *Thymus armeniacus* while another alkaloid with activating effect on ASIC3 was purified from *Laurus nobilis* leaves. The analysis of structural features of both alkaloids results in a determination of the structural core necessary for an interaction with ASICs that presents also in endogenous isoquinoline alkaloids tetrahydropapaveroline and reticuline. It is interesting but these molecules are involved in pain relief in mammals via endogenous morphine biosynthesis pathway. At physiological pH endogenous isoquinoline alkaloids is able to effectively activate hASIC3 and rASIC3 and prevent steady state desensitization of these channels. *In vivo* experiments shown the analgesic effect in CFA induced hyperalgesia animal test for both inhibitor and activators of ASICs, so the role of ASICs in the nociception process is ambiguous and requires a more detailed study.

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