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Research report

Influence of acid-sensing ion channel blocker on behavioral responses in a zebrafish model of acute visceral pain

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ABSTRACT

Acid-sensing ion channels (ASICs) play significant roles in numerous neurological and pathological conditions, including pain. Although acid-induced nociception has been characterized previously in zebrafish, the contribution of ASICs in modulating pain-like behaviors is still unknown. Here, we investigated the role of amiloride, a nonselective ASICs blocker, in the negative modulation of specific behavioral responses in a zebrafish-based model of acute visceral pain. We verified that intraperitoneal injection (i.p.) of 0.25, 0.5, 1.0, and 2.0 mg/mL amiloride alone or vehicle did not change zebrafish behavior compared to saline-treated fish. Administration of 2.5% acetic acid (i.p.) elicited writhing-like response evidenced by the abnormal body curvature and impaired locomotion and motor activity. Attenuation of acetic acid-induced pain was verified at lower amiloride doses (0.25 and 0.5 mg/mL) whereas 1.0 and 2.0 mg/mL abolished pain-like responses. The protective effect of the highest amiloride dose tested was evident in preventing writhing-like responses and impaired locomotion and vertical activity. Collectively, amiloride antagonized abdominal writhing-like phenotype and aberrant behaviors, supporting the involvement of ASICs in a zebrafish-based model of acute visceral pain.

1. Introduction

Pain is an unpleasant phenomenon that includes sensory, cognitive, and emotional processing [1]. Pain experience often adversely affects daily activities and work status, reducing well-being sensation [2,3]. Animal experimental models have been validated to understand the mechanisms involved in nociception [4,5]. It is well established that mechanical, thermal, and/or chemical stimulation are noxious stimuli that act on specific nociceptors, eliciting pain responses [6].

In vertebrates, the pH is finely maintained across a narrow range and a fall from physiological level often lead to neuronal excitation [7]. Acid-sensing ion channels (ASICs) are sodium permeable ion channels and low pH sensing trimeric protein complexes usually located in both peripheral and central nervous systems [8]. Acid is a well-known algogen which reportedly elicits pain in both animal models and humans via activation of ASICs [8]. The genes encoding ASICs in the animal genome are ASIC1–ASIC5 [9]. ASICs play pivotal roles in numerous physiological and pathological conditions via rapid alterations in the synaptic pH, including pain sensation, fear, anxiety, learning, epilepsy, and neuronal degeneration [10,11]. Thus, ASICs may constitute prospective therapeutic targets of great importance to regulate pain responses [12].

Amiloride is a synthetic pyrazine-carbonyl-guanidine derivative with diuretic and natriuretic properties [13]. The ability of amiloride to effectively enter biological and simulated membranes has been associated with the acid-base properties of the guanidium moiety in its structure [13]. The mechanism of action of amiloride is often attributed to its non-discriminative low affinity pore-blockage effect on ASIC

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