SHORT COMMUNICATION

Functional role of bitter taste receptors agonists in mesenteric and coronary arteries in a rat model of genetic obesity

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ABSTRACT

Bitter taste receptors (*TAS2Rs*) are expressed in extra-oral tissues including systemic arteries, however, their function regulating vascular contractility during health and disease still unclear. Thus, the major aim of this study is to investigate the role of TAS2R agonists, in the regulation of mesenteric and coronary arteries in a rat model of genetic obesity, metabolic syndrome and tunicamycin-induced Sarcoplasmic Reticulum (SR) stress. Arterial mesenteric and coronary rings from Obese Zucker Rats (OZR) and their counterpart Lean Zucker Rats (LZR) or arterial mesenteric and coronary rings from Tunicamycin-Induced Sarcoplasmic Reticulum Stress Rats (T-SRS) were mounted in micro vascular myographs for isometric force recordings. Concentration-dependent curves were obtained for denatonium, chloroquine and, quinine on phenylephrine precontracted rings, in the absence or presence of specific inhibitors of Nitric Oxide (NO) synthesis (L-NOARG), or Cyclooxygenases (COX) (indomethacin). The effects of TAS2R agonists modulating the excitatory or inhibitory neurotransmission were assessed by Electrical Field Stimulation (EFS) in the absence or presence of a threshold concentration of denatonium. EFS experiments were performed on basal and pre- contracted rings. The effects of denatonium on the basal tension of coronary arteries were also examined in Zucker and T-SRS rats. Denatonium, chloroquine, and quinine induced concentration-dependent relaxations of mesenteric arteries in both LZR and OZR. The effect of denatonium to induce vasorelaxation was more pronounced in OZR than in their controls LZR. Inhibition of NO synthesis but not COX reduced the effects of denatonium to induce vasorelaxation.

INTRODUCTION

The relaxant effects of denatonium in mesenteric arteries of T-SRS rats were more potent than the effects of chloroquine, however, t-here were no differences when comparing to control groups. EFS-induced relaxation of mesenteric arteries appeared to be reduced under Stress Conditions SR. A threshold concentration of denatonium recovered back the EFS-induced vasorelaxation to values like that observed in arteries from control rats. Denatonium evoked concentration-dependent contractions on the basal. The tension of the coronary arteries of both groups OZR and LZR and in T-SRS and their controls, without differences between groups. The concentrations of denatonium required to produce contractions of the coronary arteries were higher than those doses required to produce relaxation of the mesenteric arteries. The present results suggest that TAS2R receptors are functional and regulate mesenteric ontractility. Therefore, TAS2Rs agonists may have important effects on the regulatory function of vascular contractility, which may be helpful in the development of pharmacological tools targeting TAS2R for the treatment of vascular disorders related to metabolic syndrome c and stress. Significant advances have been made in the past decade in mapping the distributions and the physiological functions of extra-oral bitter taste receptors TAS2Rs in non-gustatory tissues. In particular, it has been found that TAS2Rs are expressed in various muscle tissues and activation of TAS2Rs can lead to muscle cell relaxation, which suggests that TAS2Rs may be important new targets in muscle relaxation therapy for various muscle-related diseases. So far, however, there is a lack of potent extra-oral TAS2R agonists that can be used as novel drug agents in muscle relaxation therapies. Interestingly, Traditional Chinese Medicine (TCM) often characterizes a drug's property in terms of five distinct flavors (bitter, sweet, sour, salty, and pungent) according to its taste and function, and commonly regards "bitterness" as an intrinsic property of "good medicine." In addition, many bitter flavored TCM is known in practice to cause muscle relaxation after long-term use, and in lab experiments, the compounds identified from some bitter flavored TCM do activate TAS2Rs and thus relax muscle cells. Therefore, it is highly possible to discover very useful extra-oral TAS2R agonists for muscle relaxation therapies among the abundant bitter compounds used in bitter flavored TCM. With this perspective, we reviewed in literature the distribution of TAS2Rs in different muscle systems with

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a focus on the map of bitter flavored TCM which can regulate muscle contractility and related functional chemical components. We also reviewed the recently established databases of TCM chemical components and the bioinformatics software which can be used for high-throughput screening and data mining of the chemical components associated with bitter.