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Contribution of natural products to the discovery of the transient receptor potential (TRP) channels family and their functions

João B. Calixto*, Candida A.L. Kassuya, Eunice André, Juliano Ferreira[1]

Departamento de Farmacologia, Universidade Federal de Santa Catarina, Campus Universitário-Trindade, Bloco D-CCB-Cx. Postal: 476-CEP: 88049-900-Florianópolis, SC, Brazil

Abstract

Members of the transient receptor potential (TRP) family of nonselective cation channels are involved in several pathological and physiological conditions. The search for the molecular targets for naturally occurring substances, especially from plants, allowed the characterization of many TRP channels. In fact, attempts to understand the hot and painful action of the vanillyl group containing compounds capsaicin (from *Capsicum* sp.) and its ultrapotent analogue resiniferatoxin (RTX, from *Euphorbia* sp.) led to the cloning of the vanilloid receptor (TRPV1) 7 years ago. TRPV1 is found in sensory fibers and functions as a molecular integrator of several painful stimuli, being especially stimulated during inflammation. Since TRPV1 is involved in several pathological conditions, selective ligands or modulators of this channel are substances of potential interest to treat such diseases. Once again, natural products seem to be also interesting sources of compounds that might be prototype TRPV1 ligands. The cloning of TRPV1 also enabled the discovery of other members of the TRPV family of channels. Similar to TRPV1, these receptors function as molecular detectors of physical and chemical stimuli, such as innocuous and noxious heat, as well as mechanical force. Recently, novel TRP channels sensitive to low temperatures also have been cloned, namely, TRPM8 and TRPA1. Such channels are also activated by naturally occurring substances but knowledge of their involvement in health and disease is in its infancy. In the present review, we focused on the contribution of natural products to the discovery of TRP channels and to the development of novel drugs to treat pathological conditions in which these channels are involved.
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Keywords: Natural products; Capsaicin; Resiniferatoxin; TRPV1; TRPM8; TRPA1

Abbreviations: ANKTM, ankyrin-like protein with transmembrane; ATP, adenosine triphosphate; Ca^{2+}, calcium; cDNA, complementary deoxyribonucleic acid; CGRP, calcitonin gene-related peptide; CHO cells, Chinese hamster ovary cells; COX, cyclooxygenase; DAG, diacylglycerol; DRG, dorsal root ganglion; HEK cells, human embryonic kidney cells; hTRP, human TRP; IP_3, inositol trisphosphate; LOX, lipoxygenase; mRNA, messenger ribonucleic acid; mTRP, mouse TRP; nAchR, nicotinic acetylcholine receptors; NGF, nerve growth factor; P2Y, purine receptor; PGE_2, prostaglandin E_2; PIP_2, phosphatidylinositol bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLA_2, phospholipase A_2; PLC, phospholipase C; rTRP, rat TRP; RTX, resiniferatoxin; THC, Δ^9-tetrahydrocannabinol; TG, trigeminal ganglion; TM, transmembrane; TRP, transient receptor potential.

Contents

* Corresponding author. Tel.: +55 48 331 9491, +55 48 331 9764; fax: +55 48 337 5479.
E-mail addresses: calixto@farmaco.ufsc.br, calixto3@terra.com.br (J.B. Calixto), ferreiraj99@bol.com.br (J. Ferreira).
[1] Current address: Biochemistry Course, Department of Chemistry, Universidade Federal de Santa Maria, Santa Maria, Brazil.

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1. Introduction

The use of natural products, especially those derived from medicinal plants, is a traditional form of providing relief from illness and can be traced back over 5 millennia in several civilizations. Over the years, natural products have contributed enormously to the development of important therapeutic drugs used currently in modern medicine (Cragg et al., 1997; De Smet, 1997; Shu, 1998). About 25% of all available modern drugs are derived directly or indirectly from higher plants (for review, see De Smet, 1997). Among the most interesting examples of this, are morphine and salicylates that allowed the development of major classes of the analgesic drugs, namely, opioids and non-steroidal anti-inflammatory drugs (for review, see Calixto et al., 2000, 2001). However, the potential of natural products as sources for new drugs is still largely unexplored since only a small fraction of plants, animals and microorganisms have been so far investigated phytochemically or biologically (Hamburger & Hostettmann, 1991). Besides the clinical use of natural products or their derivatives to treat disease, these substances have over the years also been important tools for the discovery of new targets such as receptors, enzymes, transporters, or ion channels involved in relevant physiological and pathological processes. As we will show in this review, natural products have indubitably played a relevant role in the recent identification of the mammalian transient receptor potential (TRP) family. In this article, we review recent developments in the study of TRP channels with emphasis on the role of naturally occurring substances that have highlighted these channels as new potential targets for the development of therapeutic drugs. For a better understanding of this point, we will also present a brief description of TRP channels themselves. However, it is

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