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Minireview

Essential oils components as a new path to understand ion channel molecular pharmacology

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ABSTRACT

The discovery and development of new drugs targeting voltage-gated ion channels are important for treating a variety of medical conditions and diseases. Ion channels are molecular nanostructures expressed ubiquitously throughout the whole body, and are involved in many basic physiological processes. Over the years, natural products have proven useful in the pharmacological assessment of ion channel structure and function, while also contributing to the identification of lead molecules for drug development. Essential oils are complex chemical mixtures isolated from plants which may possess a large spectrum of biological activities most of them of clinical interest. Among their bioactive constituents, terpenes are small to medium-sized components and belong to different chemical groups. Various reports have drawn our attention to the fact that terpenes are novel compounds targeting voltage-gated ion channels. The purpose of this review is to provide a focused discussion on the molecular interaction between monoterpenes and phenylpropenes with voltage-gated ion channels in different biological scenarios.

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Introduction

Ion channels are integral membrane proteins designed to catalyze ion flux and, as a consequence produce changes in the membrane potential. These molecular nanostructures are present in all types of cells but they have a very important role in excitable cells where they are the main actors responsible for the generation of action potentials. Action potentials are the result of the activity of many different types of ion channels working in concert to carry information from one cell to another in a very controlled way.

There is much information available about the function of ion channels (Catterall 2010). Usually, we separate ion channels in two major super-families, voltage-dependent and ligand-dependent ion channels.

They are involved in a plethora of distinct physiological processes such as: neurotransmitter release, excitation–contraction coupling, excitation–transcription coupling, control of gene expression, cell development and so on. Therefore, we can argue that the normal ion channels' activity (or function) is crucial for the maintenance of health. Another important point is the realization that ion channel dysfunctions could lead to serious pathological disorders compromising the whole organism. In 2006 the US Drug Administration approved 18 new molecular compounds and two of them had their primary mode of action attributed to ion-channel modulation indicating that ion channels are very attractive and promising drug discovery targets (Dunlop et al., 2008).

In this way one would think that these molecular bio-structures are important pharmacological targets for natural-based chemical

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compounds looking at the development of new therapeutic strategies. In order to validate this saga, highly selective and potent antagonists or even agonists are a prerequisite (Bulaj 2008).

Drug discovery efforts posed by the medicinal chemists' community have discovered a rather small number of molecules that modulate ion channels function. Taking all of that in mind, the understanding of how these molecules actually interacts with ion channels are of great interest. Consequently, electrophysiological techniques are extremely useful for the characterization of the biological activity of isolated compounds. Electrophysiological approaches are enormously rich in terms of acquired information and have been considered as the gold-standard assay.

Essential oils: new source for new molecules

In search for new sources of natural molecules that modulate ion channel behavior, essential oils are both promising and challenging. Plant essential oils are typically composed of volatile aromatic terpenes and phenylpropanoids. These lipophilic substances are classified as monoterpenes and sesquiterpenes based on the number of isoprene units (two and three respectively) besides the phenylpropanoids, which are made up of C6C3 units. These molecules freely cross cellular membranes and may serve various signaling roles inside the cell. In addition, there are some reports indicating that essential oil plant components are active towards ion channels and receptors (Gonçalves et al., 2008; de Almeida et al., 2008; Alves et al., 2010). Apart from rational drug design and novel synthetic efforts, natural products are still been investigated for novel chemical structures that may interact with known and unknown pharmacological targets. The pharmacology of ion channels has become a complex research area and as far as we understand the mechanisms controlling ion channel functioning, more potential drug targets are being disclosed.

At this point it is worth to remind that over the decades, natural products have undoubtedly contributed to the development of new drugs currently used in clinical practice. More importantly, these remarkable molecules have also been important tools for the discovery of new pharmacological targets such as receptors and/or ion channels (Vriens et al., 2008). One of the most relevant examples is the transient receptor potential (TRP) family of ion channels. This area is very active and there are excellent reviews covering various aspects including the role of natural products in the discovery and pharmacological characterization of TRP channels (for review see Calixto et al., 2005; Vriens et al., 2008) and therefore we will not cover in detail this topic.

In this mini-review we will focus on medicinal compounds which modulate ion channels present in different physiological systems.

Constituents of essential oils that acts in the central and peripheral nervous system

The potential use of essential oils as modulators of ion channels in the treatment of several diseases is indeed exciting. Although most of the published studies quote the popular use of essential oils in the treatment of several nervous system disorders, just a few studies (approximately 3% in a PUBMED search) described the activity and toxic effects of its major components on the nervous system (de Sousa et al., 2006; Goncalves et al., 2010). Only a small fraction of those studies deals with the interaction between terpenes and ion channels.

Linalool is a monoterpene that has been the subject of a number of studies and it is one of the major constituents of several essential oils isolated from different plant species. Linalool has been reported to have diverse biological and pharmacological activities (Celik and Ozkaya, 2002; Peana et al., 2002; Bickers et al., 2003; de Almeida et al., 2009). There are reports showing that linalool acts on the central nervous system but through a yet unrevealed mechanism. Linalool shares high lipid solubility with other lipid soluble odorants that directly affect ion channels activity (Kawai et al., 1997; Kawai, 1999; Kawai and Miyachi, 2000) suggesting that linalool could interact with certain types of ion channels by changing the lipid membrane environment. It was already been described that this monoterpene has sedative effects in vertebrates including humans (Buchbauer et al., 1991; Sugawara et al., 2000), and that the inhalation of linalool can lead to a significant reduction of motility in mice (Jirovetz et al., 1991). Other possible applications for linalool are as pain modulator, anticonvulsant, hypnotic and hypothermic agent. Elisabetsky et al. (1995) described that linalool inhibits glutamatergic neurons and later Sugawara et al. (2000) observed that it also affected human brain beta waves amplitude. Earlier studies in newt olfactory receptor cells, newt retinal neurons and rat cerebellar Purkinje cells demonstrated that linalool non-selectively but reversibly suppressed the voltage-gated currents (Narusuye et al., 2005). In the same report it was shown that linalool reduced KCl-induced intracellular Ca^{2+} elevation without affecting the machinery responsible for intracellular Ca^{2+} signaling (Narusuye et al., 2005).

The pharmacological effects of linalool on somatic sensory neurons have been studied in more detail by Leal-Cardoso's group (Leal-Cardoso et al., 2010). The authors provided a reasonable number of experimental findings to conclude that inhibition of the voltage-gated Na^+ channels is probably the major mechanism by which the neuronal excitability is impaired.

Taken all together, we may suggest a possible mechanism of action that could be attributed to linalool as a main frame to explain its various effects. As a consequence of a significant reduction in Ca^{2+} influx there is an important neurotransmitter release inhibition in the presynaptic terminals. Similarly, but not independently, linalool could elicit a blockade of voltage-gated Na^+ channels causing a premature termination of the action potential generation which per se would lead to diminution of neurotransmitter release by exocytosis. Presumably, the body of evidences in the literature support the general mechanism pointed out above but it is clear that further studies are necessary to explore in more detail how linalool is acting.

Eugenol, a phenylpropene derivative, is widely used in dentistry as local anesthetic, analgesic, anti-microbial and anti-inflammatory agent (Hashimoto et al., 1988; Ohkubo and Kitamura, 1997; Pizzo et al., 2006). In a series of papers from Oh's group it was postulated that the analgesic effects of eugenol in rat dental afferent neurons could be related to its inhibitory effect on voltage-gated Na^+ channels (Park et al., 2006) and on high voltage-activated Ca^{2+} channels (Lee et al., 2005). Surprisingly, both effects did not require TRPV1 activation (Lee et al., 2005; Park et al., 2006). Interestingly, when mammalian central nervous system is acutely exposed to eugenol it causes a general depressant activity leading to sedation, reduction of convulsions induced by electroshock and hypothermia Dallmeier and Carlini (1981).In fact, very little is known about eugenol's mechanism (s) of action especially in the central nervous system.

However, it is well known that eugenol blocks rat sciatic nerve compound action potentials probably by acting on the voltage-dependent Na^+ channels. At high concentrations (2 mM) and during brief applications eugenol blocked the action potential without interfering in the resting membrane potential or membrane input resistance. However, at low concentrations (0.6 mM) and longer applications the authors observed a significant reduction in the input membrane resistance which, as discussed by the authors, raises the possibility of a secondary effect involved in the reduction of neuronal excitability when eugenol was present (Moreira-Lobo et al., 2010). Elucidative studies also showed that eugenol inhibited thermal nociception and capsaicin-induced thermal hyperalgesia in orofacial area indicating that this phenylpropene derivative could also be used for other pathological pain conditions (Park et al., 2009). At this point a note of caution should be presented concerning the activation of TRPV1 channels by eugenol which could evoke excitation of