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Review

The vanilloid receptor TRPV1: Role in cardiovascular and gastrointestinal protection

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ABSTRACT

It has been shown that the transient receptor potential channel vanilloid type 1 (TRPV1) is able to sense a vast range of stimuli and exerts multiple functions under physiological or pathophysiological conditions. TRPV1 not only plays a fundamental role in pain signaling but also involves in many other physiological or pathophysiological functions including the beneficial effects on cardiovascular and gastrointestinal function. It has been found that TRPV1 could be activated by endogenous ligands such as anandamide, N-arachidonoyl dopamine and N-oleoyldopamine or by exogenous agonists such as capsaicin and rutaecarpine. Since capsaicin-sensitive sensory nerves (rich in TRPV1) are densely distributed in the cardiovascular and gastrointestinal system, activation of TRPV1 either by endogenous ligands or by exogenous agonists has been repeatedly reported to exert hypotensive effects or protective effects against cardiac or gastrointestinal injury through stimulating the synthesis and release of multiple neurotransmitters such as calcitonin gene-related peptide and substance P. Therefore, TRPV1 is not only a prime target for the pharmacological control of pain but also a useful target for drug development to treat various diseases including cardiovascular and gastrointestinal diseases. However, considering the contribution of TRPV1 to the development of inflammation in the gastrointestinal tract, the potential side effects of TRPV1 agonist cannot be neglected while in seeking and developing the novel TRPV1 agonists.

Contents

1. Introduction

1.1. The transient receptor potential vanilloid 1

Transient receptor potential (TRP) channels are a family of ion channels that have been recognized to sense a vast range of stimuli from chemical substances (such as cations) to chemical factors (such as noxious heat). Most TRP channels are comprised of 6 membrane-spanning helices with intracellular N- and C-termini and are expressed throughout the body. So far, based on their potential ligands, TRPs have been subdivided in at least 6 main subclasses: TRPC (C stands for canonical), TRPV (V stands for vanilloid), TRPM (M stands for melastatin), TRPP (P stands for polycystin), TRPML (ML stands for mucolipin) and the TRPA (A stands for ankyrin) (Leung et al., 2008; Nagy et al., 2004).

The transient receptor potential vanilloid 1 (TRPV1), also named vanilloid receptor subtype 1 (VR1) or capsaicin receptor due to its sensitivity to vanilloids or capsaicin, is an ion channel expressed predominantly in sensory nerves (Caterina et al., 1997). TRPV1 has

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been found widely distributed in different tissues and organs (Gunthorpe and Szallasi, 2008; Nagy et al., 2004). The cloned TRPV1 is a ~95-kDa protein. Its N- and C-termini are intracellular and the N-terminus has three ankyrin repeat domains. The predicted structure of TRPV1 shows that it has six transmembrane domains with an additional intramembrane loop connecting the fifth and sixth transmembrane domains (Nagy et al., 2004). TRPV1 is currently under intense investigation in health and disease because this ion channel is able to sense a vast range of stimuli and exerts multiple functions under physiological or pathophysiological conditions. There are plenty of reports that TRPV1 could be activated by noxious temperature, low extracellular pH and diverse lipid derivatives, and is particularly sensitive to vanilloid molecules, including capsaicin (De Petrocellis and Di Marzo, 2005; Dhaka et al., 2009; Liu and Simon, 2000).

1.2. Agonists for TRPV1

Since TRPV1 has been thought as a sensor for various stimuli, it is reasonable to speculate that there exist endogenous ligands or agonists for it. It has been shown that some endogenous arachidonic acid derivatives and lypoxygenase products exerted highly potent stimulatory effect on TRPV1, from which several candidates have been identified as the possible endogenous ligands or agonists for TRPV1 (De Petrocellis and Di Marzo, 2005; Hwang et al., 2000; Jia and Lee, 2007). The fatty acid amide arachidonylethanolamide, also known as anandamide, is previously known as a cannabinoid receptor 1 (CB_1) agonist. Recent studies showed that anandamide was also able to activate human and rat TRPV1 (Bianchi et al., 2006; Panlilio et al., 2009). In rat isolated small mesenteric arteries, it has been reported that anandamide induced the vasorelaxation through activation of TRPV1, which was potentiated by N-palmitoylethanolamide (PEA) and N-oleoylethanolamide (OEA) (Ho et al., 2008). However, there has been a long debate about its possible role as the natural endogenous agonist for the TRPV1 receptor because in the lower concentration range anandamide produced antinociception and inhibited the effect of resiniferatoxin (a capsaicin analog) although it mimicked the effects of capsaicin in higher doses (Szolcsanyi et al., 2004).

N-arachidonoyl dopamine (NADA) and N-oleoyldopamine (OLDA), the other fatty acid amides, were also identified as TRPV1 receptor agonists (Chu et al., 2003; De Petrocellis et al., 2004). NADA produces TRPV1-mediated thermal hyperalgesia and it is similar in potency to capsaicin in a variety of assays of TRPV1 activity. Unlike NADA or anandamide, OLDA was only a weak ligand for CB_1 receptors, suggesting that it is a selective TRPV1 agonist. Moreover, it is able to significantly induce TRPV1-mediated thermal hyperalgesia with the potency greater than that of NADA. Whereas the potency of NADA is 20-fold more than that of capsaicin or anandamide (Chu et al., 2003), therefore OLDA is likely the most powerful agonist for TRPV1 so far. It is worth to mention that NADA together with anandamide have been also reported to participate in the modulation of T-type voltage-gated calcium channel currents (Ross et al., 2009).

As mentioned above, TRPV1 is also often called capsaicin receptor because it is highly sensitive to capsaicin, an active ingredient of chili peppers. Capsaicin, an acylamide derivative of homovanillic acid, is the well-known exogenous agonist for TRPV1 (Szolcsanyi, 2004). The compound consists of three functional moieties: vanillyl, acylamide and alky. Since its isolation in the mid-nineteenth century, capsaicin has been shown to selectively act on sensory fibers, which are usually referred to the capsaicin-sensitive sensory nerves. Interestingly, capsaicin-sensitive nerve endings could be stimulated as well as destroyed by a sufficiently high dose of capsaicin (Mozsik et al., 2005). Now, capsaicin is not only widely used as chemical tool in research but also used for some clinical purposes (Knotkova et al., 2008). It is of note that capsaicin is hazardous in cases of skin or eye contact, ingestion or inhalation. Severe over-exposure to pure capsaicin can result in death. Due to the strong neurotoxicity effect of capsaicin, other exogenous agonists of TRPV1 with lower toxicity are under intensive investigation.

Rutaecarpine (8, 13-dihydroindolo-(29, 39: 3, 4) pyrido (2,1-b) quinazolin-5(7H)-one) is a major quinazolinocarboline alkaloid isolated from Chinese herbal drug Wu-Chu-Yu, which has long been used for the treatment of gastrointestinal disorders, headache, amenorrhea, and postpartum hemorrhage in traditional Chinese medicine (Deng et al., 2004). It has been reported that rutaecarpine has extensive pharmacological actions from beneficial effects on cardiovascular and gastrointestinal functions, anti-inflammatory and anti-thrombotic activity to anti-cancer and anti-obesity effects (Lee et al., 2008). The mechanisms underlying the pharmacological actions of rutaecarpine have not been fully elucidated. Previous reports suggested that the anti-inflammatory activity of rutaecarpine may be due to its inhibitory effects on cyclooxygenase 2 (COX2) (Moon et al., 1999). Recent studies have shown that rutaecarpine was able to activate TRPV1 (Chen et al., 2009; Kobayashi et al., 2001). The multiple pharmacological actions of rutaecarpine might be mediated by the released neurotransmitters such as calcitonin gene-related peptide (CGRP), substance P (SP) etc. through activation of TRPV1 (Hu et al., 2002). The properties of the potential ligands or agonists for TRPV1 were summarized in Table 1.

It is well accepted that TRPV1 plays a fundamental role in pain signaling (Knotkova et al., 2008; Lambert, 2009). TRPV1 agonists such as capsaicin cause pain in humans and pain behavior in animals whereas disruption of the TRPV1 gene or block of TRPV1 by its antagonists markedly attenuate thermal hyperalgesia (Roberts and Connor, 2006; Willis, 2009). Recently, there is emerging evidence that TRPV1 is also involved in many other physiological or pathophysiological functions: 1) it plays a major role in body-temperature maintenance (Gavva, 2008); 2) it participates in the regulation of feeding and body weight (Leung, 2008; Motter and Ahern, 2008); 3) it contributes to respiratory inflammation and disease (Geppetti et al., 2006; Takemura et al., 2008). In addition, the reports from others and ours have demonstrated that activation of TRPV1 by its agonists exerted beneficial effects on cardiovascular and gastrointestinal function (Hu et al., 2003a; Hu et al., 2003b; Nozawa et al., 2001; Wang, 2005; Wang and Wang, 2005; Ward et al., 2003). In this review, we will not intend to discuss the role of TRPV1 in pain signaling, body-temperature maintenance, fat distribution or respiratory inflammation because there are several excellent reviews that have been recently published for those topics (Gavva, 2008; Jia and Lee, 2007; Leung, 2008; Palazzo et al., 2008). Instead, we will focus on its role in cardiovascular and gastrointestinal system.

2. TRPV1 and cardioprotection

Capsaicin-sensitive sensory nerves are densely distributed in the myocardium and the coronary vascular system. It seems that capsaicin-sensitive cardiac nerves regulate a series of complex cellular events contributing to physiological and pathological myocardial function (Bell and McDermott, 1996). There were reports that sensory fibers innervating the myocardium and forming perivascular plexi of coronary arteries were able to express TRPV1 (Franco-Cereceda and Lundberg, 1988; Gulbenkian et al., 1995), activation of which by capsaicin has been shown to contribute to the development of reflex bradycardia and hypotension (Bezold–Jarisch reflex) (Aviado and Guevara Aviado, 2001). In myocardial ischemia, myocardial cells suffer from a lack of oxygen caused by inadequate coronary flood flow. The direct consequences of ischemia are a deficit in high-energy phosphate compounds and changes in glycolysis and internal pH. TRPV1 in perivascular plexi activated by low pH in the ischemic myocardium was closely related to the development of chest pain and reflectory sympathetic activation (Franco-Cereceda et al., 1993). At