Invited Review

Serotonin-induced ion channel modulations in mesenteric artery myocytes from normotensive and DOCA-salt hypertensive rats

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Abstract

Although serotonin (5-hydroxytryptamine, 5-HT) has been found to be a potent vasoconstrictor, a pivotal role of 5-HT in the control of appetite and mood control by the modulation of neuronal synapse has also been proposed. Selective 5-HT reuptake inhibitors (SSRIs) are frequently used to suppress appetite and treat depressive disorder, and the target protein of SSRIs is the 5-HT transporter (5-HTT) in the neuronal synapse. However, SSRIs may increase the free 5-HT concentration in circulating blood because platelets and vascular smooth muscles express functional 5-HTT. In addition, enhanced vasoactive action of 5-HT and alterations in 5-HT receptor subtypes have been reported in some types of hypertension. Therefore, we can infer that the use of drugs such as SSRIs in some hypertensive patients is potentially risky. Altered functional expression of ion channels in vascular smooth muscle is suggested to be a mechanism for the enhanced vasoconstriction by vasoactive agonists, including 5-HT. In this brief review, we compared the electrophysiological properties of mesenteric artery myocytes and their modulation by 5-HT between sham-operated control and deoxycorticosterone acetate (DOCA)-salt hypertensive rats.

Key words: serotonin (5-hydroxytryptamine), hypertension, ion channel, serotonin reuptake inhibitor (SSRI), mesenteric artery

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) was originally found to be a potent vasoactive agent (Page, 1952) and was reported to be closely related to the pathophysiology of some systemic and pulmonary hypertensions (Watts, 2002; Watts, 2005; Cogolludo et al., 2006). In addition, 5-
HT is now attracting interest as a neurotransmitter in the central nervous system (CNS) and gastrointestinal (GI) tract. For example, 5-HT is involved in various aspects of central neuronal regulation, including roles in emotional activity, psychiatric disease, and appetite regulation. To treat these disorders, especially to suppress appetite and treat depressive disorders, selective serotonin reuptake inhibitors (SSRIs) are frequently used (Barbey et al., 1998; Wagstaff et al., 2002). In addition, the majority of 5-HT in the human body is present in the GI system, which expresses various types of 5-HT receptor subtypes. Thus, regulating the action of 5-HT is a good strategy for reducing GI symptoms. For these reasons, drugs like selective 5-HT receptor subtype antagonists and/or agonists and SSRIs are widely used. However, as noted above, this neurotransmitter is also a strong vasoconstrictor, and an unusual increase in the plasma 5-HT concentration may cause harmful cardiovascular effects, especially in a person with hypertension. In support of this assertion, several papers recently reported enhanced vasoactive action of 5-HT in hypertensive subjects (Watts, 2002; Kim et al., 2004b). In this review, we compare the mechanisms of different vasoconstrictive actions of 5-HT in the mesenteric arteries between normotensive and hypertensive rats, especially in terms of ion channel modulations of smooth muscle cells.

**Ion channels in vascular smooth muscle and blood pressure**

The peripheral vascular resistance is an important determinant of the blood pressure and is largely regulated by the contractile status of the smooth muscle cells of small arterioles. The intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)) plays a pivotal role in the regulation of smooth muscle contraction, and the influx of Ca\(^{2+}\) is largely contributed by voltage-gated Ca\(^{2+}\) channels in vascular smooth muscle. Thus, the membrane potential (E\(_m\)) of vascular smooth muscle cells (VSMCs) is an important regulator of vascular tone and, consequently, blood pressure (Nelson and Quayle, 1995). Therefore, the modulation of ion channel function in vascular smooth muscle could potentially regulate blood pressure.

VSMCs have at least two different Ca\(^{2+}\)-permeable channels: L-type voltage-gated Ca\(^{2+}\) channels (VLCCs) and voltage-independent Ca\(^{2+}\) channels, such as receptor-operated Ca\(^{2+}\) (ROC) channels and store-operated Ca\(^{2+}\) (SOC) channels. Recently, the importance of the voltage-independent ROC and SOC in the regulation of [Ca\(^{2+}\)]\(_i\) in vascular myocytes and, therefore, in vasoconstriction has been highlighted by several researchers (Inoue et al., 2001; Jung et al., 2002; Lin et al., 2004; Yu et al., 2004; Bae et al., 2007). However, the current through the ROC and SOC channels can also induce E\(_m\) depolarization and subsequent VLCC activation, as well as the direct influx of Ca\(^{2+}\) through the ROC and SOC channels. Thus, the E\(_m\)-dependent VLCC is also an important pathway for Ca\(^{2+}\) influx in vascular myocytes and a regulator of vasoconstriction and blood pressure.

It has been well established that the E\(_m\) of vascular myocytes is largely established by K\(^+\) channels (Nelson and Quayle, 1995), and VSMCs functionally express at least four different K\(^+\) channels (Nelson and Quayle, 1995; Bae et al., 1999; Michelakis, 2002; Kim et al., 2004a; Park et al., 2005): voltage-gated (K\(_v\)), Ca\(^{2+}\)-activated (K\(_{Ca}\)), ATP-sensitive (K\(_{ATP}\)), and inward-rectifier K\(^+\) channels (K\(_{ir}\)). The major type of K\(^+\) channel contributing to the E\(_m\) appears to differ among
animal species and artery types. For example, $K_{Ca}$ current contributes to the $E_m$ in rabbit pulmonary artery myocytes (Bae et al., 1999), whereas $K_V$ current is the major regulator of the $E_m$ and $[Ca^{2+}]_i$ in rat pulmonary artery myocytes (Yuan et al., 1995). In the cerebral and coronary circulations, $K_r$ channels seem to be important in the regulation of the $E_m$ in smooth muscle cells and of myogenic tone (Knot et al., 1996; Park et al., 2005). In systemic arteries, many reports suggest that the $K_V$ current, although the molecular identity seems to be heterogeneous and is still controversial, is important in the regulation of smooth muscle $E_m$ and vascular tone, and thus peripheral resistance. $K_V$ channels are the target of many vasoactive agonists, including 5-HT (Cogolludo et al., 2003; Cole et al., 2005; Bae et al., 2006), and the functional down-regulation of these channels has been observed in many types of hypertension (Yuan et al., 1998; Jackson, 2005). The concept that $K_V$ channels regulate vasoconstriction via $E_m$ regulation is shown schematically in Fig. 1.

**Ion channels of mesenteric artery smooth muscle and mesenteric blood flow**

Mesenteric arteries have been frequently used for functional assessments of systemic arteries because they can represent systemic arteries and are easily prepared. In addition to systemic blood pressure regulation, mesenteric blood flow plays a specific role in the GI system by increasing after a meal to facilitate the transport of absorbed nutrients to the liver and adipose tissue (Bohlen et al., 1996; McDaniel et al., 2001). The mesenteric blood flow is
controlled by the mesenteric vascular resistance, and $E_m$ regulation by $K^+$ currents in mesenteric myocytes is important in mesenteric vascular resistance (Nelson et al., 1990; Cox et al., 2001; Ghisdal et al., 2001). Bae et al. (2006) recently demonstrated that the $E_m$ of mesenteric artery myocytes is under the regulation of $K_v$ currents and that the $K_v$ channels are the major target of vasoactive agonist-induced $E_m$ depolarization in rat mesenteric artery smooth muscle cells (MASMCs). Data in Figs. 2–4 show that the $K_v$ channels are the major regulator of the resting $E_m$ in rat MASMCs and that inhibition of the channels evokes very strong vasoconstriction of mesenteric arteries.

Interestingly, the blockade of $K_v$ channels by 4-aminopyridine (4-AP) in mesenteric arterial myocytes induced an anorexic effect similar to that with an SSRI and fenfluramine (McDaniel et al., 2001). It should be noted that 5-HT, whose concentration is an important regulator of appetite in the CNS, potently decreases $K_v$ currents in mesenteric artery myocytes and causes $E_m$ depolarization like 4-AP (Bae et al., 2006). This may indicate that 5-HT can cause an anorexic effect by a non-neuronal (vascular) mechanism as well as acting as an anorexic neurotransmitter in the CNS. As mesenteric arteries express the 5-HT transporter (5-HTT), SSRIs can increase the 5-HT concentration in mesenteric circulation (Ni et al., 2004; Ni and Watts, 2006). SSRIs probably increase the plasma 5-HT concentration because circulating 5-HT is mainly carried within platelets and platelets express functional 5-HTT.

It is generally observed that arteries from hypertensive animals are hyper-responsive to

**Fig. 2.** The effect of TEA and 4-AP on the resting $E_m$ and membrane currents recorded in the nystatin-perforated patch-clamp configuration. A schematic diagram of the nystatin-perforated patch-clamp configuration is shown as an inset above A. A & D. Representative recordings of the resting $E_m$, which were recorded in current clamp mode ($I = 0$) of the patch-clamp amplifier, and the effects of TEA and 4-AP. B & F. Representative membrane currents, which were elicited by depolarizing voltage steps (duration 250 ms, 10-mV increment) between −50 and +50 mV from a holding potential of −60 mV. C & F. The I-V relationships of the currents in B & E, respectively. The I values were measured at the end of 250-ms voltage pulses. From Bae et al. (2006).
vasoactive agonist compared with arteries from normotensive controls (Watts, 2002; Kim et al., 2004b), and mesenteric arteries from deoxycorticosterone acetate (DOCA)-salt hypertensive rats have been found to be hyper-responsive to 5-HT (Banes and Watts, 2001; Watts, 2002). It is interesting that anorexia and a decrease in body weight are the marked characteristics of DOCA-salt hypertensive animals (Table 1). Table 1 summarizes the body weights of 11-week-
old DOCA-hypertensive Sprague-Dawley (SD) rats compared with sham-operated control SD rats. These results warrant future study of the relationship between the anorexic effect of DOCA-salt hypertension and Kv channels in mesenteric artery myocytes.

5-HT and mesenteric artery smooth muscle ion channel regulation

The action of 5-HT is usually mediated by 5-HT receptors, and seven major subtypes of 5-HT receptors (5-HT1 to 5-HT7 receptors) have been identified. The most widespread of the receptor subtypes is the 5HT2 receptor, which is linked by G proteins to an increase in the activity of phospholipase C (PLC) and the generation of inositol triphosphate (IP3) and diacylglycerol (DAG). The 5HT1 receptor is also a G protein-coupled receptor (GPCR) and uses Gi and Gs to negatively link to a cAMP modulatory pathway (Martin, 1994; Hoyer et al., 2002). Although some studies have reported 5-HT receptors other than 5-HT2A in some types of hypertension (Russell et al., 2002; Banes and Watts, 2003), the 5-HT2A receptor appears to be primarily responsible for the vasoconstriction by 5-HT. In the pulmonary artery, 5-HT-induced Em depolarization was mediated via 5-HT2A receptors (Collaudo et al., 2006). In the mesenteric arteries, the vasoactive action of 5-HT also seems to be largely via 5-HT2A receptors (Watts, 2002). In our preliminary experiment, ketanserin inhibited both the 5-HT-induced mesenteric artery contraction and 5-HT-induced Kv current inhibition, indicating that the 5-HT2A receptor plays a role. As described above, the 5-HT2 receptor is a GPCR, which increases IP3 and DAG. IP3 induces a [Ca2+]i increase via the release of Ca2+ from the sarcoplasmic reticulum. This [Ca2+]i can induce the inhibition of Kv channels directly or indirectly via PKC activation (Shimoda et al., 1998; Bae et al., 2002). The results in Fig. 5 show that 5-HT inhibited Kv currents in rat mesenteric artery myocytes, which evoked marked Em depolarization because Kv current is the major regulator of Em in rat mesenteric arteries. Another metabolite resulting from the activation of a GPCR is DAG, which has been shown to directly activate Ca2+-permeable nonselective cation channels, possibly transient receptor potential (TRP) channels (Beech et al., 2004). In VSMCs, DAG is reported to activate TRP-like nonselective cation currents (Albert et al., 2005). Although it is not clear whether 5-HT can activate a TRP-like cation current in mesenteric artery myocytes, Bae et al. (2007) recently reported that the TRP-like cation current is clearly activated by 5-HT and is enhanced in the mesenteric arteries of DOCA-salt hypertensive rats compared with sham-operated control rats.

Ion channels in DOCA-salt hypertension and enhanced vasoconstriction by 5-HT

An excess of corticosteroids is related to hypertension (Kornel and Smoszna-Konaszewska, 1995; Gomez-Sanchez et al., 1996; Ullian, 1999), and a major proportion of patients with essential hypertension respond to therapies that mitigate the action of mineralocorticoid (MC) (Glorioso et al., 1995). The mechanism of corticosteroid-induced hypertension, however, is not yet clear. Although renal sodium retention and intravascular volume overload contribute to the attendant hypertension, especially early in the course of the disease, non-renal mechanisms such as an increase in peripheral vascular resistance appear to play an important role in its development.
5-HT-induced ion channel modulations and hypertension

Corticosteroids have been shown to potentiate the vasoconstrictor actions of vasoactive agonists such as 5-HT, NE, and angiotensin II (Fowler and Chou, 1961; Reis, 1960; Yard and Kadowitz, 1972; Berecek et al., 1980; Garwitz and Jones, 1982; Smith et al., 1987). Increased intracellular Na⁺ concentration ([Na⁺]ᵢ) in cells from hypertensive arteries has been noted in many studies (Friedman et al., 1957; Jones et al., 1964; Jones and Hart, 1975; Friedman et al., 1975; Friedman, 1979). On the basis of the interdependence of [Na⁺]ᵢ and [Ca²⁺]ᵢ via Na⁺/Ca²⁺ exchange, the mechanism of [Na⁺]ᵢ increase has been hypothesized to be an important pathogenic factor in essential hypertension. In searching for this mechanism, Kornel and Smoszna-Konaszewska (1995) found that the increased transmembrane influx of Na⁺ in VSMCs caused by aldosterone was inhibited by amiloride and cycloheximide, suggesting that aldosterone induces the increased synthesis of amiloride-sensitive Na⁺ channels. It is now known that the most likely candidates mediating Na⁺ influx in arterial smooth muscle are TRPCs (Inoue et al., 2001; Beech et al., 2004) and that TRPC6 is blocked by amiloride (Inoue et al., 2001). In addition, a series of recent studies indicates that TRPC6 is the essential component of ROC current in vascular myocytes (Inoue et al., 2001; Jung et al., 2002; Beech et al., 2004; Lin et al., 2004). These facts suggest that the direct action of corticosterone on vascular smooth muscle may contribute to the pathogenesis of DOCA-salt hypertension. Accordingly, we have suggested this non-renal mechanism of DOCA-salt hypertension in our recent paper (Bae et al., 2007). In DOCA-salt hypertensive rats, the 5-HT-induced inward current was markedly enhanced (Bae et al., 2007), which is shown in Figs.

![Fig. 5](image)
6 and 7. The parallel increases in ROC activity and TRPC6 expression in mesenteric arteries of DOCA-salt hypertensive rats (Figs. 6, 8 and 9) infer a possible role for TRPC6 in producing the increased transmembrane influx of Na⁺ and thereby hypertension. Moreover, the independent in vitro demonstration that TRPC6 expression is augmented in the presence of aldosterone (Fig.
5-HT-induced ion channel modulations and hypertension

Fig. 8. Comparison of TRPC6 expression in the mesenteric arteries of the sham-operated and DOCA hypertensive rats. Upper panel represents Western blottings for TRPC6, each lane of which was loaded with identical amounts of total proteins, and the relative intensity of the TRPC6 band from DOCA hypertensive rats was normalized to that from sham-operated rats (bottom panel, n=3 for each). * represents $P<0.05$ vs. sham.

Fig. 9. Mineralocorticoid response and TRPC6 protein expression in A7r5 cells. A7r5 cells in triplicate were treated with 1 $\mu$mol/l aldosterone (Aldo) or with ethanol as a vehicle control (Con) for 24 h. A, Total RNA from A7r5 cells was analyzed for MR expression by RT–PCR (upper panel). MR, mineralocorticoid receptor; RPL19, ribosomal protein L19. A7r5 cells were transfected with a construct containing a glucocorticoid response element driving expression of the luciferase gene and treated as indicated. After treatment, luciferase expression was determined (bottom panel). B, Total protein (20 $\mu$g) from A7r5 cells was prepared for Western blotting. Membranes were probed with anti-TRPC6 antibody, and reprobed with anti-actin antibody (upper panel). The relative intensity of the TRPC6 band was normalized to that of $\beta$-actin (bottom panel). Values are expressed as the means ± SEM. *$P<0.05$ vs. control. All experiments were repeated at least twice. From Bae et al. (2007).
suggests that elevated TRPC6 expression could be a primary response to elevated aldosterone in this model, rather than an epi-phenomenon of the raised blood pressure. These results indicate that the increase in vascular smooth muscle [Na⁺], associated with hypertension may be, at least in part, due to the direct up-regulation of TRPC6 in vascular smooth muscle by corticosteroids. In addition to TRPC6, we believe that other members of the TRP super-family are able to contribute to the enhanced ROC in DOCA-salt hypertension. Although TRPC6 is a good candidate for the molecular identity for the enhanced ROC current in DOCA-salt hypertension, some discrepancies still exist. The I-V relationship of the enhanced ROC current was usually outwardly rectifying in the E_m range between −100 and +60 mV under K⁺-free conditions (Fig. 7). However, an inwardly rectifying I-V relationship was frequently observed in some MASMCs (Fig. 6 and also see Fig. 3 of Bae et al., 2007). Although the reason is not clear yet, differences in heteromerization among the cell population may be responsible because TRPC channels probably function as tetramers. In fact, in A7r5 cells, Soboloff et al. (2005) showed the outwardly rectifying I-V relationship of ROC current, whereas Jung et al. (2002) reported the doubly rectifying I-V relationship (inwardly rectifying between the E_m range of −100 and +50 mV), although both studies suggested that TRPC6 was the major component of ROC in A7r5 cells.

Closing remarks

The use and abuse of SSRIs and similar drugs are expected to increase in response to an increasing need for weight control and treatment for depressive disorders. It should be noted that 5-HTT is expressed not exclusively in CNS neuronal synapses but also in VSMCs and circulating platelets. In addition, the vascular responsiveness to 5-HT is markedly enhanced in hypertension, with significant alterations of ion channels in VSMCs. Thus, drugs that affect the metabolism of 5-HT (like SSRIs) should be used with caution, especially in patients with pre-existing hypertension.

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