REVIEW

Pharmacological implications of the Ca^{2+}/cAMP signaling interaction: from risk for antihypertensive therapy to potential beneficial for neurological and psychiatric disorders

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Abstract

In this review, we discussed pharmacological implications of the Ca^{2+}/cAMP signaling interaction in the antihypertensive and neurological/psychiatric disorders therapies. Since 1975, several clinical studies have reported that acute and chronic administration of L-type voltage-activated Ca^{2+} channels (VACCs) blockers, such as nifedipine, produces reduction in peripheral vascular resistance and arterial pressure associated with an increase in plasma noradrenaline levels and heart rate, typical of sympathetic hyperactivity. Despite this sympathetic hyperactivity has been initially attributed to adjust reflex of arterial pressure, the cellular and molecular mechanisms involved in this apparent sympathomimetic effect of the L-type VACCs blockers remained unclear for decades. In addition, experimental studies using isolated tissues richly innervated by sympathetic nerves (to exclude the influence of adjusting reflex) showed that neurogenic responses were completely inhibited by L-type VACCs blockers in concentrations above 1 μmol/L, but paradoxically potentiated in concentrations below 1 μmol/L. During almost four decades, these enigmatic phenomena remained unclear. In 2013, we discovered that this paradoxical increase in sympathetic activity produced by L-type VACCs blocker is due to interaction of the Ca^{2+}/cAMP signaling pathways. Then, the pharmacological manipulation of the Ca^{2+}/cAMP interaction produced by combination of the L-type VACCs blockers used in the antihypertensive therapy, and cAMP accumulating compounds used in the antidepressive therapy, could represent a potential cardiovascular risk for hypertensive patients due to increase in sympathetic hyperactivity. In contrast, this pharmacological manipulation could be a new therapeutic strategy for increasing neurotransmission in psychiatric disorders, and producing neuroprotection in the neurodegenerative diseases.

Abbreviations

ACh, acetylcholine; ACs, adenylyl cyclases; CICR, Ca^{2+}-induced Ca^{2+}-release; ER, endoplasmic reticulum; FCCP, carbonylcyanide p-(trifluoromethoxy) phenylhydrazone; IBMX, 3-isobutyl 1-methylxanthine; IP$_3$R, inositol trisphosphate receptor; MIT, mitochondria; PDEs, phosphodiesterases; PKA, protein kinase A; RyR, ryanodine receptors; SERCA, sarcoendoplasmic Ca^{2+}-ATPase; SHR, spontaneously hypertensive rats; VACCs, voltage-activated Ca^{2+} channels.

Introduction

A series of experiments initiated 60 years ago using chromaffin cells as cellular model originated the concept of stimulus-secretion coupling to explain neurotransmitter release and hormone secretion. This concept was initially derived from the study of cat adrenal gland perfused with acetylcholine performed by Douglas and Rubin in the 1960s (Douglas and Rubin 1961). The discovery that increase in the citosolic Ca^{2+} concentration ($[Ca^{2+}]c$) was a basic requirement for exocytosis in adrenal chromaffin cells was made by Baker and Knight (1978). The most direct demonstration of relationship between a rise in $[Ca^{2+}]c$ and rapid exocytosis derived from the study performed Neher and Zucker (1993) using photoreleased caged Ca^{2+} in adrenal chromafin cells, which revealed the multiple Ca^{2+}-dependent steps of exocytosis.

In addition to Ca^{2+}, some studies showed that cAMP increases transmitter release at many synapses in autonomic nervous system of vertebrate, including sympathetic and parasympathetic ganglion neurons, and yet increases catecholamine secretion from adrenal chromaffin cells (Chern et al. 1988). Although the cellular and molecular mechanisms involved in these facilitatory actions of cAMP on the exocytosis of neurotransmitter and hormones are unclear, the pieces of evidence suggest that this intracellular messenger can thus participate in fine regulation of exocytosis due to its modulatory action on the intracellular Ca^{2+} signals.

In fact, the hypothesis for a functional interaction between the intracellular signaling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP interaction) has been extensively studied in myriad cells and tissue systems. Generally, this interaction results in synergistic effects on cell functions (Cooper et al. 1995; Bruce et al. 2002; Halls and Cooper 2011; Antoni 2012) and occurs at the level of adenylyl cyclases (ACs) or phosphodiesterases (PDEs). Recent data suggest that compartmentalization of ACs may also cause functional compartmentalization and oscillation of the cAMP levels. The more precise and specific compartmentalization takes place with several ACs in proximity to voltage-activated Ca^{2+} channels (VACCs). Thus, in excitable cells, Ca^{2+}-regulated ACs are modulated by Ca^{2+} entry through VACCs (Fagan et al. 2000). Ca^{2+} also regulates the activity of several PDEs, an issue that nevertheless has been studied to a lesser extent (Bender and Beavo 2006). The specific function of PDEs and their interaction with Ca^{2+} likely contribute to the generation of cAMP microdomains. This is described in detail in a recent study that examined the response of two PDE1 isoforms to Ca^{2+} influx through store-operated Ca^{2+} channels (Goraya et al. 2008).

The Ca^{2+}/cAMP interaction has particularly been extensively studied at the Ca^{2+} channels of the endoplasmic reticulum (ER) (Wagner et al. 2008; Lanner et al. 2010; Yule et al. 2010). Correlated molecular and pharmacological analysis showed that in rat adenohypophyseal corticotrope cells, Ca^{2+} mobilized from ryanodine-sensitive ER Ca^{2+} stores [via ryanodine receptors (RyR) channels] suppressed cAMP synthesis induced by physiological concentrations of corticotropin-releasing factor, and that the plausible cell target of Ca^{2+} is AC9 (Antoni 2012). Activation of RyR channels and the consequent release of Ca^{2+} into the cytoplasm may be regulated by cAMP through RyR-associated kinase/phosphatase complexes (Antoni 2012). Phosphorylation of RyR by protein kinase A (PKA), and also inositol trisphosphate receptor (IP_3R) at submaximal IP_3 concentrations, may increase the open probability of ER Ca^{2+} stores, amplifying Ca^{2+}-induced Ca^{2+} release (CICR) mechanism and cellular responses (Antoni 2012).

Ca^{2+}/cAMP interaction has been demonstrated in various types of secretory cells such as pancreatic acini (Giovannucci et al. 2000), parotid acini (Bruce et al. 2002), blowfly salivary glands (Fechner et al. 2013), airway epithelial cells (Lee and Foskett 2010), muscle cells such as cardiac (Marks 2013) and skeletal myocytes (Fuller et al. 2010), and hepatocytes (Chatton et al. 1998), suggesting that this functional interaction importantly participates in regulation of cellular response in various cell types. Recent evidences suggest that Ca^{2+}/cAMP interaction participates of exocytosis regulation in neurons and neuroendocrine cells (Marcantoni et al. 2009; Wang and Zhang 2012; Bergantin et al. 2013). Then, dysfunctions of cellular homeostasis of Ca^{2+} and/or cAMP in these cells could result in the dysregulation of Ca^{2+}/cAMP interaction and exocytotic response.

Our previous studies indicated that dysfunctions of cellular homeostasis of Ca^{2+} in the sympathetic neurons and adrenal chromaffin cells are responsible for incrementing of exocytotic release of catecholamine and sympathetic hyperactivity in animal models of arterial hypertension (Miranda-Ferreira et al. 2008, 2009, 2010; de Pascual et al. 2013). Our recent study showed that Ca^{2+}/cAMP interaction participates in regulation of neurotransmitter release from sympathetic nerves (Bergantin et al. 2013), suggesting that dysregulation of this interaction could contribute to sympathetic hyperactivity in arterial hypertension.

Since 1975, several clinical studies have reported that acute and chronic administration of L-type VACCs blockers, such as nifedipine, produces reduction in peripheral vascular resistance and arterial pressure associated with an increase in plasma noradrenaline levels and heart rate, typical of sympathetic hyperactivity (Grossman and
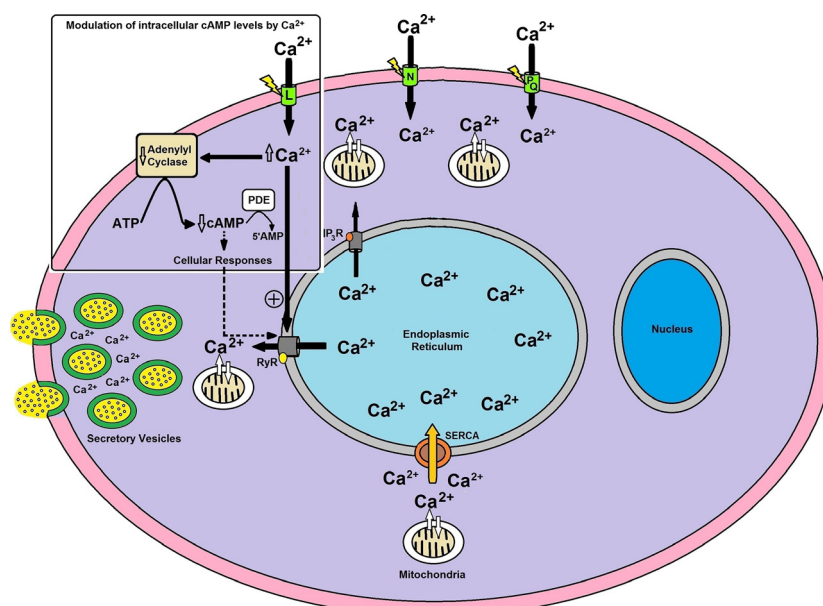
Messerli 1998). Despite this sympathetic hyperactivity has been initially attributed to adjust reflex of arterial pressure, the cellular and molecular mechanisms involved in this apparent sympathomimetic effect of the L-type VACCs blockers remained unclear for decades. In addition, experimental studies using isolated tissues richly innervated by sympathetic nerves (to exclude the influence of adjusting reflex) showed that neurogenic responses were completely inhibited by L-type VACCs blockers in high concentrations (>1 μmol/L), but paradoxically potentiated in concentrations below 1 μmol/L (Kreye and Luth 1975; French and Scott 1981; Moritoki et al. 1987; Rae and Calixto 1989). During almost four decades, these enigmatic phenomena named by us as "calcium paradox" remained unclear. In 2013, we discovered that this paradoxical increase in sympathetic activity produced by L-type VACCs blocker is due to Ca²⁺/cAMP interaction (Bergantin et al. 2013).

Then, the pharmacological manipulation of the Ca²⁺/cAMP interaction produced by combination of the L-type VACCs blockers used in the antihypertensive therapy, and cAMP accumulating compounds used in the antidepressive therapy such as rolipram, could represent a potential cardiovascular risk for hypertensive patients due to increase in sympathetic hyperactivity. In contrast, this pharmacological manipulation could be a new therapeutic strategy for increasing

neurotransmission and producing neuroprotection in the neurodegenerative diseases such as Alzheimer disease and Parkinson, and psychiatric disorders such as depression. In this review, we discussed pharmacological implications of the Ca²⁺/cAMP signaling interaction in the antihypertensive and neurological/psychiatric disorders therapies (Fig. 1).

Pharmacological implications of the Ca²⁺/cAMP interaction: role in the paradoxical effects of L-type Ca²⁺ channel blockers

Analyzing MEDLINE database from 1975 to 1996, Grossman and Messerli (1998) found 63 clinical studies involving 1252 hypertensive patients reporting alterations of sympathetic activity produced by acute and chronic administration of L-type VACCs blockers, such as verapamil. Grossman and Messerli (1998) showed that acute administration of L-type VACCs blockers produced a significant reduction in mean arterial pressure (by 13.7 ± 1.1%) positively correlated ($r = 0.59$, $P < 0.01$) with increment of plasma noradrenaline levels (by 28.6 ± 2.5%), and increase in heart rate (by 13.7 ± 1.4%). This study suggests that this apparent sympathomimetic effect of L-type VACCs blockers could directly be involved in the increase in morbidity and mortality

Figure 1. Intracellular signaling pathways mediated by Ca²⁺ and cAMP (Ca²⁺/cAMP interaction). When excitable cells such as neuroendocrine cells are stimulated by membrane depolarization, Ca²⁺ influx mediated mainly by L-type VACCs promotes an increase in [Ca²⁺]c, which inhibits AC activity, and in turn, reduces cytosolic cAMP concentration ([cAMP]c) and cAMP-mediated cellular responses.

associated with chronic use of these drugs. Despite this sympathetic hyperactivity has been initially attributed to adjust reflex of arterial pressure, the cellular and molecular mechanisms involved in this paradox of the L-type VACCs blockers remained unclear for decades.

Experimental studies using isolated tissues richly innervated by sympathetic nerves as a study model of sympathetic neurotransmission (Caricati-Neto et al. 2004; Burnstock 2009; Burnstock et al. 2010; Bergantin et al. 2013; Koslov and Andersson 2013; Bomfim et al. 2014) and to exclude the influence of adjusting reflex (e.g., rodent vas deferens) showed that nerve-mediated responses were completely inhibited by L-type VACCs blockers in high concentrations (>1 μmol/L), but paradoxically potentiated in concentrations below 1 μmol/L (Kreye and Luth 1975; French and Scott 1981; Hidalgo et al. 1983; Moritoki et al. 1987; Rae and Calixto 1989; Hata et al. 1992).

In fact, since 1975 it was reported that, despite the well-known effect of verapamil to block neurogenic contractions mediated by sympathetic nerves, lower concentrations of verapamil caused a prominent augmentation of those contractions (Kreye and Luth 1975). In agreement with this, French and Scott (1981) observed that verapamil unexpectedly potentiated nerve-mediated contractions in prostatic portion of vas deferens, but antagonized those of the epididymal end. These authors provided no reasonable explanation for this paradoxical finding. Six years later, another study reported these nerve-mediated contractions were enhanced by verapamil and diltiazem (Moritoki et al. 1987). This study concluded that this effect was due to an agonist effect of verapamil on presynaptic L-type VACCs, thus enhancing neurotransmitter release stimulated by Ca²⁺ entry (Moritoki et al. 1987). From these reports, we may already suggest that this paradoxical phenomenon relies on increases in secretory vesicles of sympathetic nerves. Two years later, a fourth study appeared showing that nerve-mediated contractions of vas deferens were augmented by both, L-type VACCs blockers and activator BAY K 8644 (Rae and Calixto 1989). Interestingly, these authors observed that verapamil (30 μmol/L) markedly enhanced potentiation of nerve-mediated contractions caused by BAY K 8644 in a supra-additive fashion, suggesting that verapamil and BAY K 8644 enhance nerve-mediated contractions by different mechanisms, discrediting the hypothesis of an agonist effect of verapamil on presynaptic L-type VACCs.

In a recent report from our laboratory, we could reproduce those earlier observations in the nerve-mediated contractions of the rat vas deferens: at lower concentrations verapamil elicited a tiny augmentation, while at higher concentrations of this blocker caused full inhibition of the contractions (Bergantin et al. 2013). The interesting finding was that, as the high verapamil concentrations, various cAMP accumulating compounds, such as PDEs inhibitors like rolipram and 3-isobutyl 1-methylxanthine (IBMX), and ACs activator forskolin, depressed the nerve-mediated contractions of vas deferens; however, in the presence of cAMP accumulating compounds, the lower concentrations of verapamil caused a drastic augmentation of the nerve-mediated contractions. The inhibition of ACs by SQ 22536 attenuated the enhanced nerve-mediated contractions, suggesting that Ca²⁺/cAMP interaction could possibly explain the paradoxical effects of combined verapamil plus cAMP accumulating compounds (Bergantin et al. 2013).

On the basis of classical receptor theory, combination of two drugs with inhibitory action produces inhibitory effects (Rang 2006). Thus, potentiation of nerve-mediated contractions of the rat vas deferens by simultaneous administration of verapamil and cAMP accumulating compounds is an experimental finding unexpected in accordance with receptor theory. Interaction between intracellular signaling pathways mediated by Ca²⁺ and cAMP could explain in a more consistent way this pharmacological phenomenon. The idea of interaction between intracellular signaling pathways mediated by Ca²⁺ and cAMP was supported by means of various experimental setups. For example, potentiation of nerve-mediated contractions produced by combination of verapamil and cAMP accumulating compounds was prevented by reduction in [cAMP]c caused by ACs inhibitor SQ 22536 or depletion of Ca²⁺ storages of ER by Ca²⁺ reuptake blocker thapsigargin (Fig. 2). These results suggest that blockade of Ca²⁺ influx through L-type VACCs by verapamil produces a reduction in [Ca²⁺]c, leading to increase in ACs activity, that in turn, results in increase in [cAMP]c (Fig. 2). The increase in [cAMP]c stimulates Ca²⁺ release from ER, and consequently increased cellular response, as shown in Figure 2.

Considering that cAMP accumulating compounds, such as rolipram, IBMX, and forskolin, classically have relaxant effects in smooth muscles, mainly through the inhibition of phosphorylation of smooth muscle myosin (Roberts and Dart 2014), and that high concentrations of L-type VACCs blockers inhibit neurotransmission in the sympathetic synapses, the result we obtained was clearly unexpected: the combination of these drugs produced a definite potentiation of nerve-mediated contractions, instead of the expected inhibition (Fig. 3).

Obviously, these results cannot be attributed to an artifact, considering that by using multiple combinations of drugs (e.g., rolipram plus verapamil, IBMX plus verapamil, etc.) the paradoxical phenomenon still existed. Based on this intriguing result, we built up the "calcium
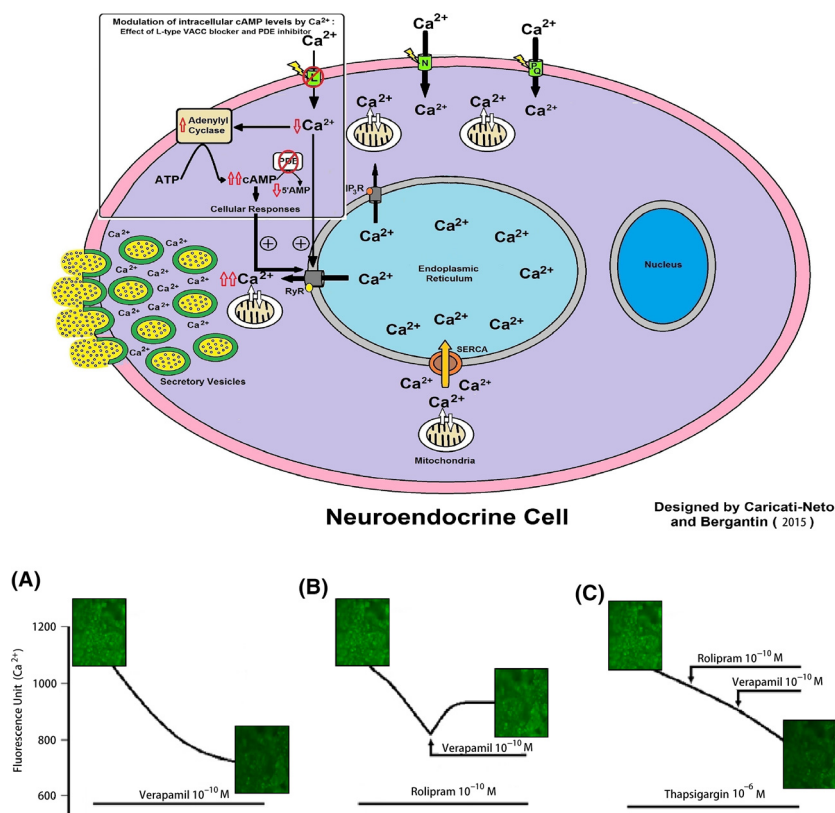
Figure 2. (A) By reducing Ca^{2+} influx and, consequently $[Ca^{2+}]_c$, L-type VACCs blockers should reduce secretion. (B) However, the reduction in Ca^{2+} entry through L-type VACCs blockers by verapamil or nifedipine may activate the Ca^{2+}–sensitive ACs, thereby causing the activation of the cAMP pathway – Ca^{2+} release from the ER. Thus, in this model we have two "antagonistic forces" driven by Ca^{2+} entry and cAMP: the channel component (fast activity) and the component of the signaling pathway (slow activity). (C) The "calcium paradox" implies a presynaptic/neuroendocrine cell reduction in Ca^{2+} entry produced by the low verapamil concentrations, removal of Ca^{2+}-dependent inhibition of ACs colocalized with L-type VACCs, augmented cAMP, increased ER Ca^{2+} release via RyR (inhibited by thapsigargin) and enhanced release of secretory vesicle. (Fluorescence images extracted from Bergantin et al. (2013) Cell Calcium - http://www.sciencedirect.com/science/article/pii/S0143416013000894). (In accordance with "author use" - Reuse of portions or extracts from the article in other works - http://www.elsevier.com/journal-authors/author-rights-and-responsibilities#author-use).

paradox" hypothesis, trying to explain the enigma that existed in sympathetic transmission since 1975 (Fig. 2). By using separately, cAMP accumulating compounds, and L-type VACCs blockers, their predominant effect could be exerted directly in the smooth muscle (postsynaptic effect), causing its relaxation. However, at presynaptic level (secretory apparatus, Fig. 2), low concentrations of L-type VACCs blockers, as well as cAMP-accumulating compounds, may have excitatory effects on synaptic transmission (Marcantoni et al. 2009). The combination of these drugs caused a synergistic effect (Ca^{2+}/cAMP interaction) at this level, so predominating the presynaptic effect, and thus enhancing transmitter release to increase muscle contraction (Fig. 2).

It seems now clear that the "calcium paradox" occurs when using low concentrations of L-type VACCs blockers (Kreye and Luth 1975; French and Scott 1981; Moritoki et al. 1987; Rae and Calixto 1989; Pirisino et al. 1993). We try to explain this fact in Figure 2, where two components associated with L-type VACCs blockers are shown: the component of channel (fast activity) and the component of signaling pathway (slow activity). At low blocker concentrations, it is plausible that the component of signaling pathways is stronger enough to overcome the effect of mild VACCs inhibition. Also, in results from our laboratory performed in bovine adrenal chromaffin cells (secretory response activity) we could clearly see this phenomenon: nifedipine may enhance their secretory activity (Rosa et al. 2011). In addition, it is plausible that the biphasic effect of BAY K 8644 on neurogenic contraction (concentration-dependent contraction and relaxation) (Fontaine and Lebrun 1988) and secretion (Garcia et al. 1984) could also be explained in the context of the "calcium paradox". At higher concentrations, the inten-
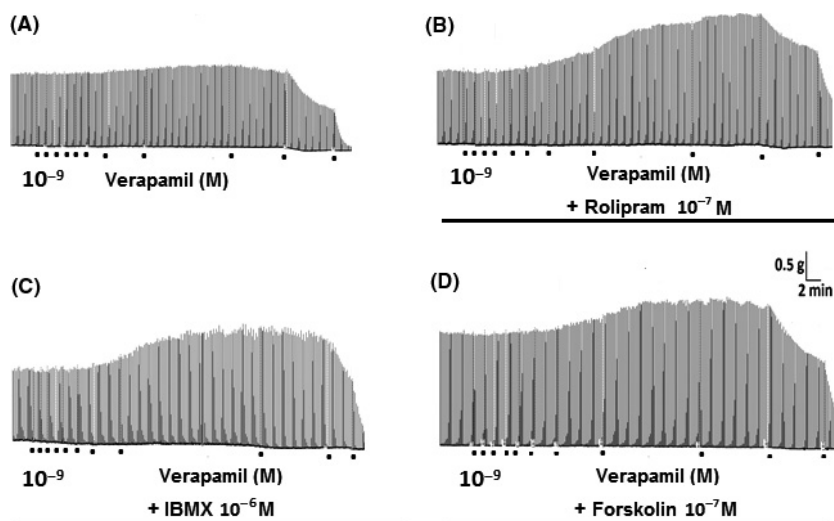
Figure 3. Effects of the verapamil, in the absence (A) and presence of rolipram (B), IBMX (C), and forskolin (D), on neurogenic contractions mediated by sympathetic nerves in rat vas deferens. These contractions were completely inhibited by verapamil in high concentrations (>1 μmol/ L), but paradoxically potentiated in concentrations below 1 μmol/L due to increase in neurotransmitter release (A). In the presence of cAMP accumulating compounds (preincubation for 15 min), the inhibitory effect of verapamil was attenuated while its facilitatory effect was significantly potentiated (B, C, and D). According to the theoretical model proposed by Bergantin et al. (2013): the reduction in Ca^{2+} influx due to L-type VACCs blocker (verapamil) combined with increase in [cAMP]c resulted in increase in neurotransmitter release from sympathetic nerves that mediates motor response of smooth muscle of the rat vas deferens. (Records of neurogenic contractions extracted from Bergantin et al. (2013) Cell Calcium - http://www.sciencedirect.com/science/article/pii/S0143416013000894). (In accordance with "author use" - Reuse of portions or extracts from the article in other works-http://www.elsevier.com/journal-authors/author-rights-and-responsibilities#author-use).

sive influx of Ca^{2+} promoted by BAYK 8644 may inhibit the constitutive activity of Ca^{2+} and cAMP signaling pathways associated with L-type VACCs, thus reducing the secretory response mediated by Ca^{2+} release from the ER (Fig. 2).

As in neurotransmission model of vas deferens, some paradoxical effects have also been recently reported to occur in adrenal chromaffin cells, an interesting model of neuroendocrine cell. For instance, in a study performed in voltage-clamped bovine chromaffin cells, the blockade of L-type VACCs with nifedipine transformed the exocytotic responses elicited by a double-pulse protocol from depression to facilitation (Rosa et al. 2011). In an earlier study, it was shown that nifedipine suppressed the endocytotic response triggered by a long depolarizing stimulus (Rosa et al. 2007). The explanation for the paradoxical effect of nifedipine could rest in the fact that inhibition of rapid endocytosis triggered by Ca^{2+} entry through L-type VACCs of bovine chromaffin cells could unmask a full exocytotic response. A second explanation may lay in the observation that Ca^{2+} entry through L-type VACCs causes the inhibition of P/Q-type VACCs (α_{1A}, Cav 2.1) (Rosa et al. 2009) that in bovine chromaffin cells greatly contribute to the control of the exocytotic release of catecholamines (Lopez et al. 1994). By blocking L-type VACCs, nifedipine could remove the Ca^{2+}-dependent inactivation of P/Q-type VACCs to enhance Ca^{2+} entry

through them, and thereby augmenting exocytosis. An additional explanation for the nifedipine paradoxical effect in chromaffin cells (Rosa et al. 2011) could be found in the context of the "calcium paradox" described in the vas deferens and in the Ca^{2+}/cAMP interaction (Bergantin et al. 2013). In agreement with these observations, recent reports (Xiong et al. 2011 and Shang et al. 2014) have observed an inhibitory effect of extracellular Ca^{2+} on Ca^{2+}-dependent exocytosis. These paradoxical findings may be explained in the context of the "calcium paradox" described in the vas deferens and in the Ca^{2+}/cAMP interaction (Bergantin et al. 2013) (Figs. 2 and 3).

Pharmacological implications of the Ca^{2+}/cAMP interaction: risk for antihypertensive therapy

It is well documented that sympathetic hyperactivity is involved in the pathogenesis of arterial hypertension. However, cellular and molecular mechanisms involved in this hyperactivity remain unknown. Using amperometric methodology to measure quantal release of catecholamine by adrenal chromaffin cells, we showed that the secretory response of spontaneously hypertensive rats (SHR) is distinct from its normotensive controls. Compared to normotensives, the secretory responses stimulated by 2-sec

pulses with ACh (1 mmol/L) and high K^+ (70 mmol/L) in SHR cells had the following characteristics: (1) double number of secretory events, (2) four fold augmentation of total secretion, (3) cumulative secretion that saturated slowly, (4) three fold higher complex events with two to four superimposed spikes that may be explained by faster spike kinetics, (5) about two to three fold higher event frequency at earlier poststimulation periods, and (6) two to five fold higher quantal content of single spikes (Miranda-Ferreira et al. 2008). These results showed that SHR cells have faster and larger catecholamine release responses, explained by more vesicles ready to undergo exocytosis and greater quantal content of vesicles.

It is also well documented that Ca^{2+} participates of different steps of exocytosis, including vesicles recruitment and docking to the plasma membrane, priming of fusion machinery and fusion of vesicles with the plasma membrane (Aunis and Langley 1999; Borges et al. 2002; Garcia et al. 2006; Garcia-Sancho and Verkhratsky 2008; Garcia-Sancho 2014). Then, the differences in secretory response between hypertensives and normotensives could be explained on the basis of distinct mechanisms of Ca^{2+} handling by adrenal chromaffin cells of SHR and its normotensive controls.

To explore the hypothesis above, we used fluorescent microscopy methodologies in adrenal medullary slices of SHR and its normotensive controls loaded with calcium fluorescent probes to measure the changes in $[Ca^{2+}]_c$, $[Ca^{2+}]_{er}$, and $[Ca^{2+}]_{mit}$ (Miranda-Ferreira et al. 2009, 2010). We found the following differences on calcium handling in SHR, as compared with its controls: (1) higher basal $[Ca^{2+}]_c$ and basal $[Ca^{2+}]_{mit}$; (2) greater $[Ca^{2+}]_c$ elevations elicited by ACh and K^+, with faster activation but slower inactivation; (3) greater $[Ca^{2+}]_c$ elevations elicited by mixture of caffeine, ryanodine, and thapsigargin and by the mitochondrial protonophore FCCP (carbonylcyanide p-(trifluoromethoxy) phenylhydrazone). The higher basal $[Ca^{2+}]_c$ and $[Ca^{2+}]_{mit}$ suggest an enhanced mitochondrial Ca^{2+} uptake, and the greater $[Ca^{2+}]_c$ elevations produced by FCCP indicates a higher mitochondrial Ca^{2+} release into the cytosol. This alteration of intracellular Ca^{2+} movements could explain the greater quantal catecholamine release responses previously detected in SHR. These studies indicated that sympathetic hyperactivity in arterial hypertension is associated with dysfunctions of cellular homeostasis of Ca^{2+} (Miranda-Ferreira et al. 2008, 2009, 2010; de Pascual et al. 2013).

In accordance with what has been mentioned in introduction, Ca^{2+} modulates ACs activity, and this mechanism involved in "calcium paradox" due to Ca^{2+}/cAMP interaction could be altered in neuroendocrine cells of hypertensives contributing to sympathetic hyperactivity and, consequently, to pathogenesis of arterial hyperten-

sion. This could have relevance to further understand the pathogenic mechanisms involved in the development of high blood pressure, as well as in the identification of new drug targets to treat hypertension.

Considering Medline database from 1975 to 1996 in which Grossman and Messerli (1998) found 63 clinical studies involving 1252 hypertensive patients reporting sympathetic hyperactivity produced by acute and chronic administration of L-type VACCs blockers, and also other reports in some hypertensive patients that nifedipine has been reported to cause sympathetic activation and a paradoxical augmentation of blood pressure (Pohar et al. 1989; Ruzicka et al. 2004; Lindqvist et al. 2007; Elliott and Ram 2011). Then, whether "calcium paradox" due to Ca^{2+}/cAMP interaction is involved in this sympathetic hyperactivity in hypertensive patients deserves special attention.

In fact, L-type VACCs blockers like verapamil and nifedipine analogous have been extensively used to reduce blood pressure in hypertensive patients, especially in combination with other drugs for treating angina or cardiac arrhythmias (Elliott and Ram 2011). In the field of drug interaction, we could also infer that a therapy involving the combination of VACCs blockers with drugs which increase [cAMP]c should be done carefully in hypertensive patients with neurological/psychiatric disorders, considering the role of sympathetic transmission in regulating vascular tone by releasing neurotransmitters into the vasculature. Then, this pharmacological interference of the Ca^{2+}/cAMP interaction could represent a potential risk for antihypertensive therapy due to increase in sympathetic hyperactivity in the cardiovascular system.

Pharmacological implications of the Ca²⁺/cAMP interaction: potential beneficial for neurological and psychiatric disorders

In contrast to deleterious effects produced by combination of L-type VACCs blockers with cAMP accumulating compounds in the cardiovascular diseases, the pharmacological implications of the Ca^{2+}/cAMP interaction produced by this drug combination could be used to enhance neurotransmission and mitigate deleterious excess Ca^{2+} influx, a condition seen in aging and neurodegenerative diseases (Kawamoto et al. 2012). These hypotheses need further investigation in experiments with animal models of disease as well as in clinical trials.

Recent studies have showed that chronic treatment with rolipram together with typical antidepressants has been successful in the reduction of depression symptoms due to potentiation of these antidepressants effects (Sommer et al. 1995; Li et al. 2011; Xiao et al. 2011). Considering our model in which increment of [cAMP]c

stimulates Ca^{2+} release from ER (Fig. 2), it may be plausible that the therapeutic use of the PDE inhibitor rolipram (Sommer et al. 1995; Xiao et al. 2011), in combination with low doses of verapamil to potentiate neurotransmission (as indicated in Figs. 2 and 3) in the areas of central nervous system involved in neurological/psychiatric disorders in which neurotransmission is reduced, including psychic depression, dementias like Alzheimer disease, Parkinson, and others. This new pharmacological strategy for the treatment of these neurological/psychiatric disorders could increase the therapeutic efficacy and reduce the adverse effects of the medicines currently used for treating these disorders.

In addition, considering $[Ca^{2+}]_c$ elevation and exocytosis could contribute to the neuroprotective effects (Maroto et al. 2011), it may be plausible the therapeutic use of the PDEs inhibitors (Sommer et al. 1995; Xiao et al. 2011) for neuroprotective purposes . Then, pharmacological interference of the Ca^{2+}/cAMP interaction produced by combination of L-type VACCs blockers and cAMP-accumulating compounds could enhance neuroprotective response and reduce clinical symptoms of neurological/psychiatric disorders. This new pharmacological strategy could be alternatively used for treatment of the symptoms of neurodegenerative diseases such as Alzheimer disease and Parkinson, and psychiatric disorders such as depression.

Acknowledgements

Disclosures

None declared.

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