European Journal of Pharmacology 714 (2013) 229–238

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Implicating the role of plasma membrane localized calcium channels and exchangers in stress-induced deleterious effects

Anjana Bali, Sakshi Gupta, Nirmal Singh, Amteshwar Singh Jaggi *

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147002, India

ARTICLE INFO

Article history:
Received 28 February 2013
Received in revised form
16 April 2013
Accepted 8 June 2013
Available online 21 June 2013

Keywords:
Stress
Calcium
L-type calcium channel
Na^+/Ca^{2+} exchanger

ABSTRACT

Stress-induced increase in intracellular calcium (Ca^{2+}) has been demonstrated to produce various deleterious effects in the body. The rise in intracellular Ca^{2+} (particularly neuronal) in response to stress has been mainly attributed to opening of voltage gated L-type Ca^{2+} channels. The role of P/Q-, N-, R- and T-type Ca^{2+}channels, and plasma membrane localized exchangers such as Na^+/Ca^{2+} exchanger and Ca^{2+} ATPase has also been implicated in increasing intracellular Ca^{2+} in response to stress. Stress-induced changes in Ca^{2+} currents has been mainly attributed to increased release of corticosterone (activation of glucocorticoid receptors in the hippocampus) and catecholamine release as a consequence of activation of Hypothalamic–Pituitary–Adrenal (HPA) axis and sympathetic neural system, respectively. Stress-induced increase intracellular Ca^{2+} may trigger various deleterious signaling pathway including free radical generation, apoptosis, increased synaptic release of glutamate and synthesis/release of cytotoxic cytokines that may be responsible for damaging effects associated with stress. The present review discusses the mechanisms involved in stress-induced rise in intracellular Ca^{2+} levels and subsequent implications of increased Ca^{2+} levels in stress.

Contents

1. Introduction

Stress is a state of threatened homeostasis which mobilizes a composite spectrum of adaptive physiological and behavioral response with an aim to restore the challenged body homeostasis (Jaggi et al., 2011). An exposure to stress stimulus induces various

* Corresponding author. Mobile: +91 9501016036.
E-mail address: amteshwarjaggi@yahoo.co.in (A.S. Jaggi).

0014-2999/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejphar.2013.06.010

changes in the body including alteration in behavior, autonomic functions and hyper-activation of the hypothalamo–pituitary–adrenal (HPA) axis (Van de Kar and Blair, 1999). Stress triggers endogenous neuroadaptive signaling in the different body organs, particularly in the neurons to restore homeostasis. However, failure to adapt (during persistent excessive stress) produces various deleterious effects and results in development of anxiety and depression.

Calcium (Ca^{2+}) is a versatile cellular messenger and it regulates various essential neuronal functions including the synaptic transmission, gene expression and synaptic plasticity processes (Hidalgo and Carrasco, 2011). On the contrary, its key role in the pathophysiology of number of disease states including neuropathic pain of different etiology (Jaggi and Singh 2011), dementia (López-Arrieta and Birks, 2000), ischemia-reperfusion injury (Hataji et al., 2010; Zhao et al., 2013), migraine (Van den Maagdenberg et al., 2010), Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, and HIV encephalopathy (Ito et al., 1996) has been very well documented. The studies have also shown that Ca^{2+} may also act as stress mediator and its role in controlling stress-induced behavior alterations and memory impairment is also speculated. Stress is associated with an increased Ca^{2+} levels in the brain synaptosomes and increased densities of Ca^{2+} channels on different brain regions including the hippocampus (Mamczarz et al., 1999). Furthermore, the beneficial role of Ca^{2+} channel blockers such as verapamil, nifedipine and nimodipine in stress-induced gastric ulceration, learned helplessness and neuroadaptive changes has also been established (Yegen et al., 1992; Saade et al., 2003). The present review describes the mechanisms responsible for an increased intracellular Ca^{2+} particularly in neurons in response to different stressors with main emphasis on plasma membrane localized channels and exchangers.

2. Possible mechanisms involved in raising intracellular Ca^{2+} levels

2.1. L-type calcium channels

L-type Ca^{2+} channels are oligoheterodimers and are composed of α1 subunit (major pore forming and voltage sensing), α2δ, γ and β subunits (modify channel gating and surface expression). Accordingly, these Ca^{2+} channels are mainly classified by α1 subunit. $Ca_v1.2$ and $Ca_v1.3$ channels are the predominant forms of Ca^{2+} channels expressed in the brain and $Ca_v1.2$ constitute about 80% of total L-type Ca^{2+} channels in the brain. These two brain localized channels are encoded by different genes, CACNA1C gene encodes Cav1.2 subunit and CACNA1D gene encodes Cav1.3 subunit (Vacher et al., 2008). The more commonly employed L-type Ca^{2+} channel blockers (verapamil, diltiazem and nifedipine) have been differentiated on the basis of their binding site, and kinetics. The pore forming α1 subunit of these channels contains four transmembrane repeat domains, each consisting of six helices (S1–S6). Each of these four domains of the α1-subunit has a pore. However, each of the four domains of this subunit is folded on itself; so that four pores (each of one domain) contributes structurally to form one functioning pore per four domains (Opie, 1996). Nifedipine like drugs (dihydropyridines) bind to the calcium channel pore, probably on S6 extending into the channel pore on the S6 side (Striessnig et al., 1991) and the binding sites may be found on three of the four transmembrane-spanning domains I, III and IV (Kalasz et al., 1993). On the other hand, diltiazem (benzothiazepine) has a distinct binding site on the αl-subunit which is probably allosterically linked to the dihydropyridines site (Opie et al., 1987; Watanabe et al., 1993) and diltiazem promotes the binding of the dihydropyridines to their specific site (Opie, 1996; Murphy et al., 1983). Verapamil like drugs (phenylalkylamines) bind to the αl-subunit (in the neighborhood of the C-terminal chain and the adjacent S6 helix) (Striessnig et al., 1990) and in contrast to diltiazem, verapamil inhibits the binding of dihydropyridines to their specific site (Glossman et al., 1985; Murphy et al., 1983).

The speed of recovery of Ca^{2+}channels after washout of Ca^{2+} channel blockers also varies depending on the nature of blocker. Verapamil permeates the membranes more readily and the channels recover more slowly after its wash out (30–60 min). On the other hand, diltiazem and nifedipine have low permeability and hence, the channels recover more quickly after the wash out of these drugs (10–20 min). Nifedipine and diltiazem are more specific Ca^{2+}channel antagonists with no effect on the other types of ion channels. In contrast, verapamil is relatively less specific and it also inhibits the fast Na^+ channels to some extent. The order of potency of these drugs in blocking the Ca^{2+} channels is nifedipine > diltiazem > verapamil (Sperelakis, 1987). Diltiazem and verapamil block the Ca^{2+}currents by binding to channels in a state-dependent fashion, i.e., inactivated channels have a high affinity for the drugs, while rested and open channels have a lower affinity (Kanaya et al., 1983). Furthermore, the degree of blockade increases with frequency of Ca^{2+} channel stimulation and membrane depolarization (more prominent for verapamil as compared to diltiazem) (Janis and Scriabine, 1983; Lee and Tsien, 1983). On the other hand, Janis and Scriabine described that nifedipine blocks the channel not only in the open state but also in its resting state (Janis and Scriabine, 1983). Furthermore, the blocking effect of nifedipine is not frequency dependent (use-dependent) as compared to verapamil and diltiazem (Sperelakis, 1987).

The studies have shown that Ca^{2+} channel blockers attenuate the various deleterious effects in acute and chronic stress models (Cai et al., 2011; Mamczarz et al., 1999; Saade et al., 2003). Generally, acute stress is associated with behavioral alterations and cellular dysfunction; while chronic persistent stress produces cellular/tissue damage. Accordingly, these blockers have been reported to attenuate the behavioral changes in acute stress models (Saade et al., 2003; Takano et al., 2012) and cellular damage (primarily neuronal) in chronic stress models (Zhu et al., 2004). However, few studies have also demonstrated the cellular/tissue damage in acute stress models of very high intensity and Ca^{2+} channel blockers are shown to decrease the acute stress-induced cellular damage (Xu et al., 2003).

The L-type Ca^{2+}channel blockers have been shown to abolish restraint stress-induced neuroadaptive response including sensitization to amphetamine (Mamczarz et al., 1999). Chronic restraint (2 h for 7 days) stress in rats has been shown to increase the densities of L-type Ca^{2+} channel in the hippocampus and pretreatment with nifedipine before restraint sessions prevents the development of stress-induced elevation of the densities of L-type Ca^{2+} channel (Mamczarz et al., 1999). Administration of nimodipine has been demonstrated to mitigate “learned helplessness” in rats (Saade et al., 2003). Zhu et al. demonstrated that the application of prenatal stress increases the intracellular Ca^{2+} ion concentration along with production of reactive oxygen species in the hippocampal CA3 region leading to neuronal damage of the brain of offspring's (Zhu et al., 2004). The same group of scientists demonstrated an increased Ca^{2+} current amplitude, current density and average integral current in offspring hippocampal CA3 neurons in prenatal stress subjected group that in turn was completely blocked in the presence of nifedipine (Cai et al., 2007). Prenatal stress-induced increase in high-voltage-activated (HVA) Ca^{2+} current in the hippocampal CA3 neurons (Cai et al., 2007) is consistent with other findings showing an increase in large total peak Ca^{2+} currents and high-threshold non-inactivating