Inhibition of Voltage-Gated Calcium Channels by Natural Alkaloids: Pharmacological and Therapeutic Effects

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Abstract: Medicinal plants are the oldest and the most common form of medication against health issues. Several studies have demonstrated that plant extracts and their secondary metabolites represent an interesting source for drug discovery. Alkaloids, a major group of naturally occurring organic nitrogen-containing bases, have been shown to be implicated in many physiological processes through the modulation of ion channels, in particular, voltage-gated calcium channels. Calcium channels are the key molecules responsible for the regulation of major intracellular processes through the mediation of calcium entry into cells in response to membrane depolarization. They are divided into two broad categories: The high (L-, N-, P-, Q- and R-types calcium channels) and the low (T-type calcium channels) threshold-activated calcium channels. However, calcium channels dysfunction can be responsible for a multitude of disorders including several forms of cancer and epilepsy. The present article point out the scientific evidence of the effectiveness of natural alkaloids extracted from common medicinal plants including Peganum harmala on the modulation of voltage-gated calcium channels as well as their pharmacological and therapeutic outcomes.

Keywords: Voltage-gated calcium channels, medicinal plants, alkaloids, Peganum harmala, β-carbolines, bisbenzylisoquinolines, isoquinolines.

1. Introduction

Traditional medicinal plants have been used since ancient time as a rescue against many health ailments. All over the globe, especially in North African countries, the use of medicinal plants has significantly supported primary health care(Jamila et al., 2014). They can provide valuable therapeutic effects against various metabolic diseases such as diabetes, cardiovascular complications and neurological disorders(Petrovska, 2012). They are readily available, affordable and have less side effects than pharmaceutical and industrial medications. Thanks to their ability to synthesize a multitude of secondary metabolites against threatening conditions and for their normal growth and development, medicinal plants represent an interesting source for drug discovery in pharmaceutical industry. Previous studies have demonstrated that plant extracts and their secondary metabolites exert their therapeutic effects through the modulation of ion channels, in particular, voltage-gated calcium channels (VGCC) (Karaki et al., 1986; Gilani et al., 1994).

Calcium is a major signaling molecule that enters excitable cells in response to action potentials and depolarizing signals. It serves as the second messenger for the initiation of a multitude of physiological events in different cell types; it can trigger a vast array of physiological roles like muscle contraction, gene transcription and cell proliferation, (Berridge et al., 2000; Berridge et al., 2003; Clapham, 2007). VGCCare the key molecules that allow calcium entry into the cells (Clapham, 2007). VGCC are divided into two major categories based on their structural and biophysical properties: High-voltage activated channels (HVA); activated by large membrane depolarizations, and Low-voltage activated channels (LVA) that open in response to small depolarizations close to resting membrane potentials (Armstrong et al., 1985). Both VGCC families share a common Cav1 subunit that consists of four homologous domains (I-IV), with each domain containing six transmembrane segments (S1-S6) and an intracellular loop that allows the selective passage of Ca²⁺ ions. The voltage variations are detected by positively charged aminoacid residues present in the segment 4 (S4) of each domain and mediate channels gating. The transmembrane domains are connected by large cytoplasmic loops and N and C termini at the cytoplasmic parts (Catterall et al., 2005a). These regions are important sites for channels regulation by endogenous factors like second messengers, G proteins and protein kinases (Zamponi et al., 1997; Chemin et al., 2007). Beside the Cav1 subunit, HVA channels comprise the intracellularβ and the transmembrane α2-δ subunits which makes of them multimeric transmembrane proteins. In contrast, LVA are monomers because they lack these functional subunits (Fig. 1) (Curtis et al., 1984; Catterall et al., 2005b). According to pharmacological and biophysical studies, VGCC involve three subtype families with different members: Cav1, Cav2 and Cav3 (Fig. 1)(Catterall et al., 2005b).The genetic distribution and the pharmacological properties of the three VGCC subfamilies are quite distinct which allow them to control a variety of physiological and pathological processes in the central and the peripheral systems.

Inhibition of calcium channel currents with specific organic compounds has been intensively under investigation as an interesting tool for defining the physiological, the biophysical and biochemical properties of calcium channels as well as for the treatment of pathological conditions such
as diabetes and epilepsy. Our aim through this present paper is to point out the effect of natural alkaloids on the modulation of VGCC as well as their pharmacological and therapeutical virtues.

**Figure 1**: Graphic representation of voltage-gated calcium channels. Representation of the high voltage-activated calcium channel complex consisting of the main pore forming α1-subunit and ancillary, β-, γ-, and α2-δ-subunits. Low voltage-activated calcium channels may be formed of only the α1-subunit. Different α1-subunits correspond to different calcium channel isoforms Cav1, Cav2 (HVA) and Cav3 (LVA). [Adapted from (Khosravani et al., 2006)].

Alkaloids are a group of naturally occurring organic nitrogen-containing bases. They are found in a large variety of flowering plants and have been shown to be implicated in many physiological processes. In 1804, the first individual alkaloid, Morphine, was isolated from the opium poppy (*Papaver somniferum*) and has been used as a powerful analgesic against pain, pointing out the potential role of alkaloids in therapy. Morphine interacts with opioid receptors and produce analgesia by hyperpolarization of interneurons, leading to a release of transmitters associated with pain transmission (Lipp, 1991). Studies in the same context have shown that Morphine-induced-analgesia is more important the presence of VGCC blockers (Kumar et al., 2010).

2. **β-carboline Alkaloids: Harmala alkaloids**

Harmaline, Harmame

The β-carbolines Harmaline and Harmame are the active principles present in the seeds of *Peganum harmala* as well as in other medicinal plants such as *Banisteriopsis caapi* (Fig. 2) (Handforth, 2012). A growing body of reports have shown the endogenous distribution of these harmal alkaloids in different mammalian tissues where they have been suggested to exert various pharmacological actions (Parker et al., 2004; Miralles et al., 2005; Herraiiz et al., 2006b; Herraiiz et al., 2006a). Harmal alkaloids have been implicated in neurodegenerative disorders but also in neuroprotective processes because of their interaction with a large array of neurotransmitter receptors and ion exchangers. They have been shown to bind GABA_A receptors (Rommelspacher et al., 1980), activate 5HT_A and 5HT_C receptors (McCormick et al., 1998), induce the impairment of Na^+ proton exchange and mitochondrial monoamine oxidase enzymes (Glennon et al., 2000; Anderson et al., 2003; Grella et al., 2003; Herraiiz et al., 2010). Furthermore, studies have demonstrated their ability to modulate ion channels (I_{Na}, I_{K}) in particular VGCC. Haraki et al. have reported that the efficiency of *Peganum harmala* in treatment of colic is due to its antispasmodic effect resulting from the inhibition of intestinal calcium channels by the harmala alkaloids especially harmaline (Karaki et al., 1986). Recent electrophysiological studies showed that harmala alkaloidsinhibitHVA (I_{Ca,L}, I_{Ca,N}) and LVA (I_{Ca,T}) currents expressed in rat dorsal root ganglion (Fig. 2)(Splletstoesser et al., 2005) and olivary neurons (Park et al., 2010; Zhan et al., 2012)over a wide range of voltage potentials and in a dose-dependant manner, indicating their potential implication in neuroprotective processes.
Figure 2: Schematic representation of the structure of harmala alkaloids; harmaline and harmane and raw traces of voltage-activated calcium channels (a-b), sodium channels (c-d) and potassium channels (e-f) after depolarisation from holding potential of −80 to 0 mV (upper trace). Currents under control conditions (black; lower traces) and after blockade of the channel currents (grey) by 100 μM harmaline (A) or 100 μM harmane (B) are superimposed. [Adapted from (Splettstoesser et al., 2005)].

Isoquinoline alkaloids

3. Berberine

Berberine is a pharmacologically active alkaloid that belongs to the group of isoquinoline alkaloids (Fig. 3). It is found in a large variety of medicinal plants including Coptis chinensis and Coptis japonica and has been used for digestive and cardiovascular disorders. Berberine triggers AMP-activated protein kinase by increasing its activity which explains its diverse beneficial effects (Lee et al., 2006). Electrophysiological studies have revealed that berberine attenuated L- and T-type currents in guinea pig ventricular myocytes (Xu et al., 1997). Recently, the alkaloid berberine was reported to inhibit P/Q-type calcium currents leading to the attenuation of glutamate release from rat cortical synaptosomes (Lin et al., 2013), a mechanism that could underlie the anticonvulsant properties of berberine (Bhutada et al., 2010).

Figure 3: Chemical structure of berberine alkaloid

Bisbenzylisoquinoline alkaloids

Bisbenzylisoquinoline alkaloids (BBA) are a group of natural products distributed in a large variety of plants including Menispermaceae, Berberidaceae and Lauraceae families (Schiff, 1991).
4. Curine

Curine is the major BBA that is isolated from the root barks of Chondrodendron platyphyllum, a medicinal plant that naturally occurs in Brazil (Fig. 4). Curine has been suggested to induce vasodilatation in rat small mesenteric arteries through the inhibition of calcium channels (Dias et al., 2002). In order to confirm the molecular mechanisms underlaying this effect, Medeiros et al. have shown, using whole-cell patch clamp technique, that curine inhibits L-type calcium channel (LTCC) currents in A7r5 vascular smooth muscle cells in a concentration-dependent manner. Curine affected the biophysical properties of LTCC by shifting the steady-state inactivation curve towards more negative membrane potentials which decreases global intracellular Ca\textsuperscript{2+} concentrations and leads to vasorelaxation in rat aorta (Fig. 5)(Medeiros et al., 2011). However, further studies on the effect of Curine on the Cav2 and Cav3 calcium channels remain to be conducted.

5. Daurisoline

Daurisoline is another interesting BBA isolated from the rhizomes of the Chinese medicinal herb Menispermum dauricum (Fig. 4). It has been traditionally used in the treatment of asthma, hypertension and epilepsy (Waldmeier et al., 1995). Daurisoline blocks neuronal NTCC by attenuating the depolarization-induced influx of calcium in presynaptic nerve terminals (Lu et al., 1990). Further electrophysiology studies have shown the blockade P/Q-type calcium channels by daurisoline (Lu et al., 1994). The mechanism by which calcium channel blockers like daurisoline inhibits glutamate release may explain in part its neuroprotective/anticonvulsant properties.

6. Tetrandrine

Tetrandrine is a BBA derived from the Chinese medicinal plant Stephania tetrandra (Fig. 4) (Zhang et al., 2009). Tetrandrine has been used as a remedy for various health problems including cardiac arrhythmia and hypertension (Liu et al., 1995; Wang et al., 1995). A growing body of reports have shown that the antihypertensive, antiarrhythmic and antimyocardial ischemia properties of tetrandrine are linked to its direct inhibition of calcium channels in neuroblastoma cells, neurohypophyseal nerve terminals, mesenteric artery and cardiac cells (Liu et al., 1995; Wang et al., 1995). King et al. demonstrated that tetrandrine blocks LTCC activity in
GH3 anterior pituitary cells by interacting with the benzodiazepine receptor of the calcium block receptor complex (King et al., 1988). Bickmeyer et al. showed that tetrandrine blocks voltage-operated calcium channels and increases intracellular calcium by blocking endoplasmic and other calcium pumps (Bickmeyer et al., 1998). Further studies revealed that tetrandrine also inhibits neuronal N-type calcium channels (Wiegand et al., 1990) and T-type calcium channels (Liu et al., 1992; Rossié et al., 1993) in different cell types with IC50 values estimated to be within 4-20 µM, indicating a large non-selective spectrum of calcium inhibition by tetrandrine alkaloid (Kwan et al., 2002).

7. Conclusions

The results of the studies of the modulation of voltage-gated calcium channels clearly showed that the alkaloids isolated from medicinal plants including *Peganum harmala* inhibit calcium channels subunits that are expressed in different tissues; a mechanism underlying a multitude of therapeutical effects including vasodilating, neuroprotective and anticonvulsant properties.

8. Abbreviations

VGCC, Voltage-gated calcium channels; LTCC, L-type calcium channels; BBA, Bisbenzylisoquinoline alkaloids.

9. Conflict of Interest

The authors declare no conflict of interest.

References


