Autonomic Neuroscience: Basic and Clinical 202 (2017) 18–27

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

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

Review

Ca^{2+} signaling and emesis: Recent progress and new perspectives

Weixia Zhong, Andrew J. Picca, Albert S. Lee, Nissar A. Darmani *

Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA 91766, USA

ARTICLE INFO

Article history:
Received 21 April 2016
Received in revised form 21 July 2016
Accepted 22 July 2016

Keywords:
Cancer
Cisplatin
Vomiting
Emesis
Antiemesis
Ca^{2+}
L-type Ca^{2+} channel
Palonosetron
Netupitant
CB_1 receptor

ABSTRACT

Cisplatin-like chemotherapeutics cause vomiting via calcium (Ca^{2+})-dependent release of multiple neurotransmitters (dopamine, serotonin, substance P, etc.) from the gastrointestinal enterochromaffin cells and/or the brainstem. Intracellular Ca^{2+} signaling is triggered by activation of diverse emetic receptors (including tachykininergic NK_1, serotonergic 5-HT_3, dopaminergic D_2, cholinergic M_1, or histaminergic H_1), whose activation in vomit-competent species can evoke emesis. Other emetogens such as cisplatin, rotavirus NSP4 protein and bacterial toxins can also induce intracellular Ca^{2+} elevation. Netupitant is a highly selective neurokinin NK_1 receptor (NK_1R) antagonist and palonosetron is a selective second-generation serotonin 5-HT_3 receptor (5-HT_3R) antagonist with a distinct pharmacological profile. An oral fixed combination of netupitant/palonosetron (NEPA; Akynzeo(®)) with >85% antiemetic efficacy is available for use in the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Cannabinoid CB_1 receptor agonists possess broad-spectrum antiemetic activity since they prevent vomiting caused by a variety of emetic stimuli including the chemotherapeutic agent cisplatin, 5-HT_3R agonists, and D_2R agonists. Our findings demonstrate that application of the L-type Ca^{2+} channel (LTCC) agonist FPL 64176 and the intracellular Ca^{2+} mobilizing agent thapsigargin (a sarco/endoplasmic reticulum Ca^{2+}-ATPase inhibitor) cause vomiting in the least shrew. On the other hand, blockade of LTCCs by corresponding antagonists (nifedipine or amlodipine) not only provide broad-spectrum antiemetic efficacy against diverse agents that specifically activate emetogenic receptors such as 5-HT_3, NK_1, D_2, and M_1 receptors, but can also potentiate the antiemetic efficacy of palonosetron against the non-specific emetogen, cisplatin. In this review, we will provide an overview of Ca^{2+} involvement in the emetic process; discuss the relationship between Ca^{2+} signaling and the prevailing therapeutics in control of vomiting; highlight the evidence for Ca^{2+}-signaling blockers/inhibitors in suppressing emetic behavior in the least shrew model of emesis as well as in the clinical setting; and also draw attention to the clinical benefits of Ca^{2+}-signaling blockers/inhibitors in the treatment of nausea and vomiting.

Contents

1. Introduction . . . 19
2. Emerging roles of Ca^{2+} in emesis . . . 19
   2.1. Emetic receptor stimulation increases intracellular Ca^{2+} concentration . . . 19
   2.2. Emetic potential of Ca^{2+} channel activators . . . 20
3. Ca^{2+} intervention: mechanisms and potential therapeutic approaches . . . 20
   3.1. Receptor antagonist antiemetic regimens such as NEPA . . . 20
   3.2. Cannabinoid CB_1 receptor agonists . . . 21
4. Perspective in developing new antiemetic candidates . . . 22
   4.1. Antiemetic efficacy of LTCC blockers in the least shrew model of emesis . . . 22
   4.2. Potentiation of anti-emetic efficacy of 5-HT_3R antagonists when combined with LTCC blockers . . . 23
   4.3. Clinical use of L-type Ca^{2+} channel blockers as anti-nausea/anti-emetic medication . . . 23
   4.4. Internal Ca^{2+} release channels: Possible targets in preventing emesis . . . 24
5. Conclusion . . . 24
References . . . 24

* Corresponding author at: Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, 309 East Second Street, Pomona, CA 91766, USA.
E-mail address: ndarmani@westernu.edu (N.A. Darmani).

http://dx.doi.org/10.1016/j.autneu.2016.07.006
1566-0702/

1. Introduction

Acute (≤24 h) and delayed (>24 h) phases of chemotherapy-induced nausea and vomiting (CINV) cause distressing effects which affect the well-being and quality of life of cancer patients receiving chemotherapy, especially cisplatin (Kottschade et al., 2016). Major neurotransmitter mechanisms underlying CINV have been subject of considerable research over the past 25 years. Chemotherapeutics such as cisplatin induce vomiting via release of a wide variety of emetic neurotransmitters/mediators (such as dopamine, serotonin (5-HT), substance P (SP), prostaglandins and leukotrienes) in both the gastrointestinal tract (GIT) and the emetic loci of the dorsal vagal complex (DVC) in the brainstem including the nucleus tractus solitarius (NTS), the dorsal motor nucleus of the vagus (DMNX) and the area postrema (AP) (Darmani and Ray, 2009; Guttuso, 2014; Ray et al., 2009a). The AP and the NTS contain large numbers of fenestrated capillaries which lack blood brain barrier and permit neurons in both areas access to circulating factors including emetogens (Rogers et al., 2006a). The NTS is a key site for integrating diverse emesis-related information from the brain as well as the GIT conveyed by the vagal afferents which terminate preferentially in the NTS and to a lesser extent in the DMNX. The DMNX sends emetic signals via efferents to the GIT and modulates vomiting behaviors (Babic and Browning, 2014; Darmani and Ray, 2009; Rogers et al., 2006a; Rojas and Slusher, 2015).

Ca^{2+} is not only one of the most universal and versatile signaling molecules, it is also an extremely important factor in both the physiology and pathology of living organisms. At rest, diverse cells have strict and well-regulated mechanisms to maintain low nM cytosolic Ca^{2+} levels (Seaton et al., 2011). Cytoplasmic Ca^{2+} concentration is a dominant factor in determining the amount of transmitter released from nerve terminals (Katz and Miledi, 1967). Thus, Ca^{2+} mobilization can be an important aspect of vomit induction since it is involved in both triggering the quantity of neurotransmitter released coupled with receptor activation, as well as post-receptor excitation-transcription coupling mechanisms (Zuccotti et al., 2011). Studies using Ca^{2+} imaging performed in vitro in the brainstem slice preparation suggest that emetic agents evoke direct excitatory effects on cytosolic Ca^{2+} signals in vagal afferent terminals in the NTS which potentiate local neurotransmitter release (Rogers et al., 2006a, 2006b; Rogers and Hermann, 2012). Therefore, chemotherapeutics including cisplatin seem to activate emetic circuits through a number of neurotransmitters released Ca^{2+}-dependently in specific vomit-associated neuroanatomical structures. In both the periphery and the brainstem, emetic neurotransmitters/mediators—such as acetylcholine, dopamine, 5-HT, SP, prostaglandins, leukotrienes, and/or histamine—may act independently or in combination to evoke vomiting (Darmani et al., 2009). In this review, we focus on the current evidence supporting the significance of Ca^{2+} signaling in emesis generation and the corresponding development of potential novel antiemetic medications, as briefly shown in Fig. 1.

2. Emerging roles of Ca^{2+} in emesis

2.1. Emetic receptor stimulation increases intracellular Ca^{2+} concentration

Excitatory receptor activation by corresponding agonists can increase cytosolic Ca^{2+} levels via both mobilization of intracellular Ca^{2+} stores (e.g. endoplasmic reticulum = ER) and influx from extracellular fluid (Suzuki et al., 2010). The evoked cytoplasmic Ca^{2+} increase may result from direct activation of ion channels, or indirectly via signal transduction pathways following G protein-coupled receptor activation. The neurokinin NK1 receptor (NK_1R) is a member of the tachykinin family of receptors which is G-protein coupled. NK_1R stimulation by substance P or corresponding selective agonists such as GR73632, can increase cytosolic Ca^{2+} concentration. In fact GR73632-induced activation of NK_1Rs can evoke intracellular Ca^{2+} release from the sarco/endoplasmic reticulum (SER) stores via Gαq-mediated phospholipase C pathway, which subsequently evokes extracellular Ca^{2+} influx through L-type Ca^{2+} channels (LTCCs) (Lin et al., 2005; Miyano et al., 2010; Suzuki et al., 2010). The serotonergic 5-HT3 receptor ($5\text{-}HT_3R$) is a Ca^{2+}-permeable ligand-gated ion channel (Hargreaves et al., 1996). Cell line studies have demonstrated that activation of $5\text{-}HT_3Rs$ by serotonin or its analogs can evoke extracellular Ca^{2+} influx into cells in a manner sensitive to both $5\text{-}HT_3R$ antagonists (tropisetron, MDL7222, metoclopramide) and LTCC blockers (verapamil, nimodipine, nitrendipine) (Hargreaves et al., 1996; Homma et al., 2006; Hutchinson et al., 2015; Ronde and Nichols, 1997; Takenouchi and Munekata, 1998). These studies suggest that both L-type- and $5\text{-}HT_3$-receptor Ca^{2+}-permeable ion channels are involved in extracellular Ca^{2+} influx evoked by $5\text{-}HT_3R$ agonists. Moreover, $5\text{-}HT_3R$ activation indirectly causes release of Ca^{2+} from ryanodine-sensitive intracellular calcium stores subsequent to the evoked extracellular Ca^{2+} influx which greatly amplifies the cytoplasmic concentration of Ca^{2+} (Ronde and Nichols, 1997). In fact our findings from behavioral studies (Zhong et al., 2014b) further support the notion of Ca^{2+}-induced Ca^{2+} release following $5\text{-}HT_3R$ stimulation, which will be discussed in more detail in Section 4.4. Other emetogens such as agonists of dopamine D_2 (Aman et al., 2007; Wu et al., 2006)-, cholinergic M_1 (Oliveira and Correia-de-Sa, 2005; Sculptoreano et al., 2001)-, histaminergic H_1 (Barajas et al., 2008; Yoshimoto et al., 1998)- and opiate μ (Ono et al., 2002; Smart et al., 1997)-receptors, as well as cisplatin (Splettstoesser et al., 2007), prostaglandins (Almirza et al., 2012; Rodríguez-Lagunas et al., 2010), rotavirus NSP4 protein (Hagbom et al., 2012; Hyser et al., 2010) and bacterial toxins (Poppoff and Poulain, 2010; Timar Peregrin et al., 1999) also possess the potential to mobilize Ca^{2+} which involve extracellular Ca^{2+} influx and/or Ca^{2+} release from intracellular pools.

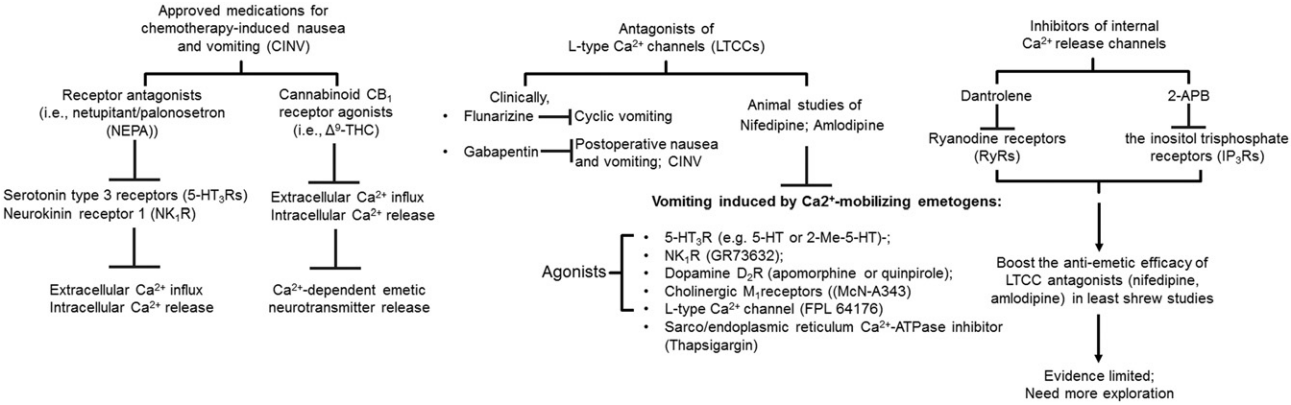

Fig. 1. Overview of evidence for Ca^{2+} signaling inhibition involved in anti-emetic actions of agents.