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Review

Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system

Keith A. Sharkey [a,*], Nissar A. Darmani [b], Linda A. Parker [c]

[a] Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada T2N 4N1
[b] Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA, USA
[c] Department of Psychology, University of Guelph, Guelph, ON, Canada

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ABSTRACT

Nausea and vomiting (emesis) are important elements in defensive or protective responses that animals use to avoid ingestion or digestion of potentially harmful substances. However, these neurally-mediated responses are at times manifested as symptoms of disease and they are frequently observed as side-effects of a variety of medications, notably those used to treat cancer. Cannabis has long been known to limit or prevent nausea and vomiting from a variety of causes. This has led to extensive investigations that have revealed an important role for cannabinoids and their receptors in the regulation of nausea and emesis. With the discovery of the endocannabinoid system, novel ways to regulate both nausea and vomiting have been discovered that involve the production of endogenous cannabinoids acting centrally. Here we review recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system, and we discuss the potential to utilize the endocannabinoid system in the treatment of these frequently debilitating conditions.

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1. Introduction

Reflex mechanisms that serve to protect a host from injury and disability represent important and frequently well-conserved adaptations to a hostile external environment. Rarely do these adaptations, such as blinking or sneezing, become "hijacked" by physiological or pathophysiological processes in the body, not involving the organ they evolved to protect. Unfortunately, that is not the case for nausea and vomiting. Nausea is an aversive experience that often precedes emesis (vomiting), but is distinct from it (Borison and Wang, 1953; Carpenter, 1990; Horn, 2008; Andrews and Horn, 2006; Stern et al., 2011). Retching and vomiting

* Corresponding author. Tel.: +1 403 220 4601; fax: +1 403 283 2700.
E-mail address: ksharkey@ucalgary.ca (K.A. Sharkey).

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lead to the forceful expulsion of gastric and/or upper intestinal contents, the primary function of which is to remove ingested materials or food that may be contaminated or potentially harmful. Nausea associated with emesis serves as an unconditioned stimulus for learning and memory; food that becomes associated with nausea and vomiting will be avoided in future encounters (Borison and Wang, 1953; Carpenter, 1990; Horn, 2008; Andrews and Horn, 2006; Stern et al., 2011).

In the natural environment, as a protective reflex, nausea and vomiting are very important adaptations found in most vertebrate species (Borison et al., 1981). However, possibly because of its importance, the sensitivity of this reflex is very low, making it easily activated. In various disease states, e.g. diabetes and labyrinthitis (Koch, 1999; Schmäl, 2013), the inappropriate activation of this reflex leads to severe and debilitating symptoms. Many central nervous system conditions, including elevated intracranial pressure, migraine headache and concussion also cause nausea and vomiting (Edvinsson et al., 2012; Mott et al., 2012; Stern et al., 2011). Nausea and vomiting are frequent, unwanted, side-effects of a range of medications used to treat a variety of conditions, notably cancer chemotherapeutic agents (Hesketh, 2005; Rojas and Slusher, 2012). Pregnancy-induced nausea and vomiting are reportedly adaptive mechanisms, but hyperemesis gravidarum can severely compromise both the health of the mother and the developing fetus (Patil et al., 2012; Sanu and Lamont, 2011; Sherman and Flaxman, 2002). Finally, motion sickness, which results from a sensory conflict between visual and vestibular stimuli, can be of immense discomfort, and severely limit certain activities (Schmäl, 2013; Yates et al., 1998). Nausea and vomiting are significant in our society and understanding them represents both an important goal and a major challenge; the former because of the substantial health implications, but the latter because it is hard to judge if an experimental animal is nauseated and commonly used laboratory animals are some of the few species that do not vomit! Nevertheless, significant progress has been made in our understanding of the processes of nausea and vomiting, which has led to new and improved pharmacological treatments for these disorders in the last 20–30 years, as described in many of the accompanying articles in this volume and previous reviews (Rojas and Slusher, 2012; Sanger and Andrews, 2006; Schmäl, 2013).

One of the oldest pharmacological remedies for nausea and vomiting is the plant cannabis (Kalant, 2001). In clinical trials, cannabis-based medicines have been found to be effective antiemetics and even surpass some modern treatments in their potential to alleviate nausea (Cotter, 2009; Tramèr et al., 2001). However, it was not until the early 1990s that the mechanism of action of cannabis was established following the cloning of the "cannabinoid" (CB) receptors (Howlett et al., 2002; Pertwee et al., 2010). The significance of this discovery was enhanced when it was realized that these receptors were part of an endogenous cannabinoid (endocannabinoid) system in the brain and elsewhere in the body (Di Marzo and De Petrocellis, 2012; Izzo and Sharkey, 2010; Mechoulam and Parker, 2013; Piomelli, 2003). The endocannabinoid system serves to modulate the expression of nausea and vomiting when activated by central or peripheral emetic stimuli (Darmani and Chebolu, 2013; Parker et al., 2011).

In this article we will outline the endocannabinoid system and then describe what is known about this system in relation to the neural circuits of nausea and vomiting. We will describe recent findings on the anti-emetic effects of cannabinoids and show how manipulation of elements of the endocannabinoid system can modify the expression of emesis. We will discuss at some length the evidence that cannabinoids and the endocannabinoid system can regulate nausea, because this is an area that has been not been considered so fully in the past. We will then briefly describe the paradoxical effect of chronic exposure to high doses of cannabis that in some people causes a cyclic vomiting syndrome. Finally, we will conclude with some future directions for this research by identifying gaps in our knowledge of the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system.

2. The endocannabinoid system

The isolation of Δ^9-tetrahydrocannabinol (Δ^9-THC) as the major psychoactive ingredient in cannabis was an important milestone in neuropharmacology (Howlett et al., 2002; Pertwee et al., 2010). This discovery provided the impetus for extensive investigations that led to an understanding of many of the central and peripheral sites of action of cannabis and ultimately to the cloning of the two G-protein coupled cannabinoid receptors; CB_1 and CB_2. CB_1 receptors are distributed throughout the central and peripheral nervous system, but also in many other sites throughout the body (Howlett et al., 2002; Pertwee et al., 2010). In the brain they are frequently expressed in high density on presynaptic nerve terminals of both inhibitory and excitatory nerves, depending on the region (Katona and Freund, 2012). CB_2 receptors are expressed on cells and organs of the immune system, but they are also found in the brain and at other sites in the body (Onaivi et al., 2012; Pacher and Mechoulam, 2011). The actions of cannabinoids can largely be accounted for by these two receptors, however, there are some well-described non-cannabinoid$_1$-, non-CB_2 receptor-mediated actions of cannabinoids. To date there is limited evidence for a third cannabinoid receptor, though some cannabinoids act at the GPR55 receptor (Pertwee et al., 2010). Whether GPR55 has any role in nausea and vomiting is not known and has not been examined to date.

Both cannabinoid receptors signal through $G_{i/o}$ proteins, inhibiting adenylyl cyclase and activating mitogen-activated protein kinase. Activation of the cannabinoid receptors limits calcium entry into cells by inhibiting N- and P/Q-type calcium currents and further inhibits cellular excitability by activating A-type and inwardly rectifying potassium channels (Howlett et al., 2002; Pertwee et al., 2010).

Shortly after the discovery of the CB_1 receptor, two endogenous cannabinoid receptor ligands, *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) were isolated (Di Marzo and De Petrocellis, 2012). Unlike many preformed intercellular mediators, endocannabinoids are made on demand when cells are stimulated with either an increase in intracellular calcium (Alger and Kim, 2011), or following metabotropic receptor activation involving $G_{q/11}$ or possibly G_s proteins (Gyombolai et al., 2012). These ligands are found in the brain and in the periphery, for example, in the gastrointestinal tract (Izzo and Sharkey, 2010), where they act at cannabinoid and other receptors (see below).

Both endocannabinoids are made by enzymatic pathways that have specific localization patterns in the brain that give important clues to their functional roles. Best characterized are the biosynthetic and degradative pathways for the formation and hydrolysis of 2-AG (Blankman and Cravatt, 2013; Long and Cravatt, 2011; Ueda et al., 2010, 2011). The most important pathway for the synthesis of 2-AG begins with activation of a phosphoinositol (PI)-phospholipase C (PLC) which hydrolyzes inositol phospholipids at the *sn*-2 position producing diacylglycerol (DAG). The hydrolysis of DAG via *sn*-1-selective diacylglycerol lipases (DAGL)-α and DAGL-β then leads to the formation of 2-AG. Alternatively, but less well characterized, is the sequential hydrolysis of PI by phospholipase A_1 to make lyso-PI which is then further hydrolysed to 2-AG by lyso PI-specific PLC. In the brain, endocannabinoid signaling is abolished in DAGL-$\alpha^{-/-}$ mice (Gao et al., 2010), suggesting this form of the enzyme is the key physiological rate limiting enzyme for 2-AG biosynthesis. The