IBRO Neuroscience Reports 15 (2023) 107–115

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

Evaluating proxies for motion sickness in rodent

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ARTICLE INFO

Keywords:
Conditioned taste aversion
Emesis
Motion sickness
Nausea
Pica
Rodent models

ABSTRACT

Motions sickness (MS) occurs when the brain receives conflicting sensory signals from vestibular, visual and proprioceptive systems about a person's ongoing position and/or motion in relation to space. MS is typified by symptoms such as nausea and emesis and implicates complex physiological aspects of sensations and sensorimotor reflexes. Use of animal models has been integral to unraveling the physiological causality of MS. The commonly used rodents (rat and mouse), albeit lacking vomiting reflex, reliably display phenotypic behaviors of pica (eating of non-nutritive substance) and conditioned taste aversion (CTAver) or avoidance (CTAvoi) which utilize neural substrates with pathways that cause gastrointestinal malaise akin to nausea/emesis. As such, rodent pica and CTAver/CTAvoi have been widely used as proxies for nausea/emesis in studies dealing with neural mechanisms of nausea/emesis and MS, as well as for evaluating therapeutics. This review presents the rationale and experimental evidence that support the use of pica and CTAver/CTAvoi as indices for nausea and emesis. Key experimental steps and cautions required when using rodent MS models are also discussed. Finally, future directions are suggested for studying MS with rodent pica and CTAver/CTAvoi models.

1. Introduction

Motion sickness (MS) is a motion- or vection (illusory self-motion)-induced malady that has been recorded as early as 700 BC by the Greek poet Semonides (Bertolini and Straumann, 2016; Diels and Howarth, 2013; Huppert, 2017; Leung and Hon, 2019); however, humans have likely experienced MS long before there was a written record (Huppert et al., 2017; Money, 1970). Nowadays, much has been known about the neurophysiology of MS, with accompanying development of many prophylactic treatments. Still, many questions remain yet to be resolved, including that regarding the neural mechanics that drive MS. Answers to these questions are key to understanding both the neuropharmacology of MS and to the development of anti-emetics.

Nausea and emesis are the major symptoms of MS. These symptoms have therefore been used as the criterion for assessing MS development (Mitchell et al., 1977a, 1977b; Money, 1970; Singh and Kuo, 2016). Rodents manifest significant behaviors such as pica (the behavior of eating non-nutritive substance) and conditioned taste aversion (CTAver) or avoidance (CTAvoi) when exposed to emetics (see the following sections). Intuitionally, the same pica and CTAver/CTAvoi responses after motion exposure led to the notion that they were the symptoms for MS in rodents (Gallo et al., 1999; Mitchell et al., 1977a, 1977b; Takeda et al., 1996). Until now, the use of rodent pica and CTAver/CTAvoi as models of MS have contributed much to understanding the neural mechanical underpinnings of MS development at both the neural circuit and molecular levels (Chen et al., 2018; Idoux et al., 2018; Inprasit et al., 2018; Machuca-Márquez et al., 2021; Sato et al., 2009; Uno et al., 2000a, 2000b; Wang et al., 2013). For instance, brain structures such as hippocampus, amygdala, cerebellum, pathways like the CCK-expressing glutamatergic vestibular-parabrachial pathway, and receptors such as transient receptor potential vanilloid type 1 (TRPV1) in the thalamus were revealed to be causally and/or symptomatically related to MS development (Inprasit et al., 2018; Machuca-Márquez et al., 2021; Sato et al., 2009; Uno et al., 2000a, 2000b).

Despite these findings, rodents lack vomiting reflex and the gastrointestinal structures that are geometrically and morphometrically suited

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https://doi.org/10.1016/j.ibneur.2023.06.006
Received 19 November 2022; Accepted 29 June 2023
Available online 8 July 2023

for emesis (Horn et al., 2013). These peculiarities raise the lingering question of whether rodent, the most commonly used experimental animal which does not vomit, can still be utilized for the study of MS. Research into the neurological substrates provided compelling evidence indicative of the mechanistic similarity between pica/CTAver/CTAvoi and gastrointestinal malaise or nausea/emesis (see review, e.g., Andrews and Horn, 2006). In this context, we reviewed published data on rodent pica and CTAver/CTAvoi to tease out the evidence that supports the physiological relevance of this model, discuss the rationale of using pica and CTAver/CTAvoi as behavioral substitutes for nausea/emesis, and examine the utility of rodent models for MS study.

2. Motion sickness study with rodents

2.1. Pathogenesis and symptoms of motion sickness

Functional integrity of the vestibular system is essential for MS development (Catanzaro et al., 2014; Lackner, 2014; Money, 1970). Vestibular afferents constantly feed back information about head orientation and movement to the brain via the central vestibular nuclear complex (VNC). This information is disseminated by VNC to diverse brain structures, subserving multiple functions across multifaceted physiological dimensions (Balaban, 2002; Balaban and Porter, 1998; Büttner-Ennever, 2000; Dieterich and Brandt, 2015; Han et al., 2021; Horowitz et al., 2005; Lackner, 2014; Ma et al., 2019; Shiroyama et al., 1999). MS may occur when conflicting sensory signals between vestibular inputs (e.g., from otolith vs semicircular canals) or between vestibular and non-vestibular proprioceptive and/or visual information about the body's ongoing position/motion are present (Fig. 1).

Subjects with MS present with a set of symptoms collectively known as MS syndrome that suggests involvement of diverse physiological systems, ranging from perception of discomforts (e.g. headache, malaise, nausea, dizziness, etc.), autonomic abnormalities (e.g. salivation, cold swearing, pallor, hypothermia, cardiovascular and pulmonary responses, etc.) to disadvantageous mental and motor manifestations (e.g. vomiting, apathy, drowsiness, fatigue, etc.) (Bertolini and Straumann, 2016; Brainard and Gresham, 2014; Catanzaro et al., 2014; Lackner, 2014; Machuca-Márquez, 2021; Money, 1970; Nalivaiko et al., 2014; Ngampramuan et al., 2014; Singh and Kuo, 2016; Yates et al., 2014). Other disorders accompanying MS also include abnormalities such as hypomotion and hypophagia (Abe et al., 2010; Borner et al., 2020; De Jonghe and Horn, 2008; Machuca-Márquez, 2021). While the extent and severity of symptoms varies between individuals, those susceptible to MS generally experience nausea and/or emesis that are preceded and accompanied by prodromal autonomic responses such as pallor, (cold) sweating, vasoconstriction, vasopressin release, and increased salivation in addition to stomach awareness (e.g., gastric dysrhythmia and proximal grastric relaxation), malaise and drowsiness (Brainard and Gresham, 2014; Catanzaro et al., 2014; Horn, 2008; Horn et al., 2013; Singh and Kuo, 2016; Yates et al., 2014. More references available on the web).

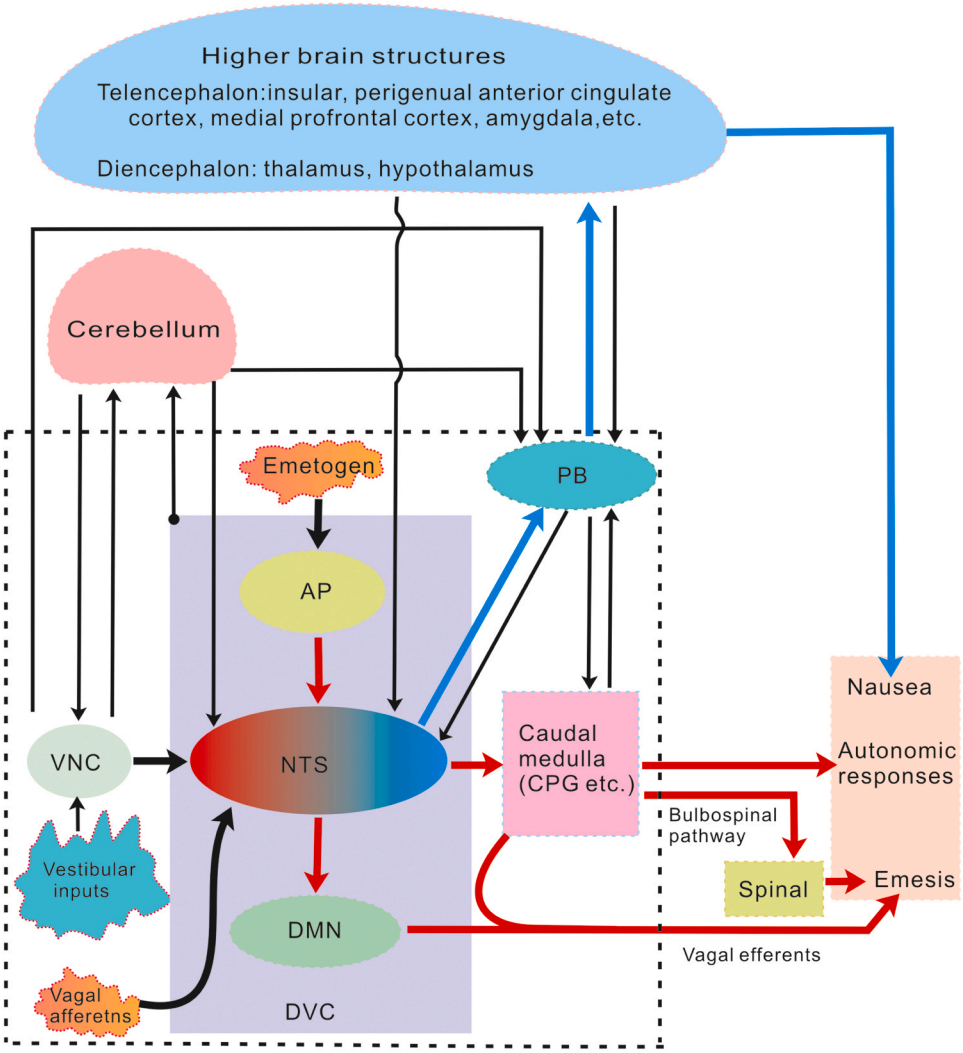

Fig. 1. Putative neural circuitry for nausea and emesis. Red arrows denoted the primary neural pathways implicated in vomiting, whereas blue arrows denote those related to pathogenesis of nausea. Detailed connections have been omitted for simplicity. Structures boxed by dashed lines are located in the brainstem. Caudal medullary neurons that participate in emetic pathophysiology include those located in the dorsolateral reticular formation (lateral tegmental field), medial medullary reticular formation (magnocellular tegmental field), BÖtzinger/ventral respiratory group, rostral nucleus ambiguus/retrofacial nucleus, and ventral lateral medulla. Abbreviations: AP, area postrema; CPG, central pattern generator; DMN, dorsal motor nucleus of vagus; DVC, dorsal vagal complex, including AP, nucleus of solitary tract (NTS) and DMN.
PB, parabrachial nucleus; VNC, vestibular nuclear complex (adapted from Balaban and Porter, 1998; Belkacemi and Darmani, 2020; Hornby, 2001; Napadow et al., 2013; Zhong et al., 2021).

2.2. Hallmark symptoms of motion sickness

Among the aforementioned symptoms, nausea and emesis are signature characteristics of MS (Brainard and Gresham, 2014; Mitchell et al., 1977b; Money, 1970); and therefore, a smattering of nausea/emesis helpful to understanding of Ms is to be described below, without the effort on an extensive and in-depth discussion.

In general, nausea and emesis are common signs and symptoms frequently known to signal gastrointestinal complaints, with the former representing unpleasant feeling and the later a reaction of throwing up. From the evolutionary perspective, nausea and vomiting function as a defense mechanism for the organism to avoid and/or mitigate gastrointestinal illness caused by ingested-pathogens or toxic chemicals (see review, Zhong et al., 2021). These digestive-relevant afflictions may implicate various etiological conditions, including infections, brain disorders and challenging movements, bodily chemical changes (as of reproductive hormone), medication (e.g., as in cancer chemotherapy and radiation therapy), food poisoning, emotional stress, or pain (Fig. 1).

It is worthy to note that, although oftentimes present in tandem, nausea and vomiting are nonetheless mediated by divergent neural pathways that partially overlap in their neural constituents (Balaban and Porter, 1998; Belkacemi and Darmani, 2020; Hornby, 2001; Napadow et al., 2013; Singh and Kuo, 2016; Yates et al., 2014; Zhong et al., 2021) (Fig. 1). In addition, behavioral reactions evoked by nausea and emesis may also differ. Reflexes, as exhibited by rodents, such as conditioned gaping, chin rubbing, salivation and drooling, and even the posture like "lying-on-belly" may characterize nausea, whereas gagging and retching are more typical of emesis (Chambers, 2018; Horn, 2008; Horn et al., 2013; Meachum and Bernstein, 1990; Parker, 2003; Snijders et al., 2021; Zaman et al., 2000). However, despite being distinct physiological processes, nausea and emesis were often described en masse without technical differentiation by previous authors, especially in studies using rodents. Herein, lay the difficulty in discriminating between nausea and emesis that were indexed behaviorally by the non-communicatory animals.

In the context of MS, both nausea and emesis are triggered essentially requiring vestibular inputs (Fig. 1). Briefly, vestibular signals, together with vestibular-activated top-down afference, converging onto the dorsal vagal complex (DVC) are sent to the nucleus of solitary tract (NTS). Signals from NTS and dorsal motor nucleus of vagus (DMN) jointly trigger emesis by subsequent activation of central pattern generator (CPG) in the brainstem and motor neurons in the spinal cord (Belkacemi and Darmani, 2020; Du Sert et al., 2012; Hornby, 2001; Koga et al., 1998; Lawes, 1990; Singh and Kuo, 2016; Yates et al., 1998; Zhong et al., 2021). Perception of nausea is fulfilled via ascending pathways from NTS to parabrachial nucleus (PB), hypothalamus and many other higher brain structures involving insular cortex, pregenual anterior cingulate cortex and medial prefrontal cortex, amygdala, and putamen etc. (Alhadeff et al., 2015; Catanzaro et al., 2014; Napadow et al., 2013; Singh and Kuo, 2016) (Fig. 1). Of note, chemo-induced nausea/emesis is caused by direct activation of receptors in DVC and/or those in visceral organs innervated by vagal nerve, unlike vestibular-induced MS (Fig. 1).

2.3. Behavioral alternatives to nausea/emesis in rodents

Human and other emetic species such as dog, cat, squirrel monkey, and house musk shrew (*Suncus murinus)* possess the feature of vomiting when exposed to provocative motion, and thus are ideal experimental subjects for MS studies aiming to disclose the physiology of MS and test candidate therapies (Chan et al., 2007; Chen et al., 2018; Cluny et al., 2008; Crampton and Lucot, 1985; Javid and Naylor, 2001, 2002, 2006; Okada et al., 1995; Rudd et al., 1999, 2018). By contrast, the species lineage Rodentia (including rat and mouse) phylogenetically lacks the ability to vomit (Horn et al., 2013). Can rats and mice therefore be used to study MS? Use of rodent models possess many advantages, including lower cost, ease of handling, extensive knowledge of their contextual biology, and, perhaps most importantly, availability of genetically engineered animal models that facilitate in-depth investigation. Fortunately, decades of research has indicated that Rodentia presumably evolved pica and CTAver/CTAvoi, the behavioral expressions of nauseous/emetic condition, serving as ways of defense similar to emesis by diluting the ingested-toxicants and repulsively avoiding the new falvored/tasted food that may cause gastrointestinal poisoning, respectively (Du Sert et al., 2012; Lin et al., 2014; Mitchell et al., 1977b; Pebsworth et al., 2019).

Behavioral representations of rodent gastrointestinal illness, especially pica and CTAver/CTAvoi, have long since been reported and widely used as indications and/or measurements of rodent nauseous and emetic condition by hundreds of studies. We herein only impress on our readers the close pica/CTAver/CTAvoi-illness relationship through "droplets in a stream" of literature. Readers are suggested to refer to the websites for related topics and monographs for in-depth knowledge on pica, CTAver and CTAvoi, as well as their applications to dissecting mechanisms underlying gastrointestinal illness.

2.3.1. Pica

The validity of rodent pica as a proxy for nausea/emesis is supported by evidence from multiple studies (e.g., Andrews and Horn, 2006; Borner et al., 2020; De Jonghe and Horn, 2008; De Jonghe et al., 2009; Li et al., 2018; Nakajima, 2018, 2020; Sugino et al., 2021; Takeda et al., 1995a, 1995b; Watson and Leitner, 1988; Watson et al., 1987; Yamamoto et al., 2004, 2007, 2011). Early on, Mitchell, et al. (1976) showed that lithium chloride was able to induce pica in rats. Later, numerous studies showed that rats/mice responded with pica and/or CTAver/CTAvoi to the causative drugs (with efficacious dose) of human nausea/emesis and emetic animal retching. Theses drugs include lithium chloride, nicotine, copper sulfate, apomorphine, veratrine, resiniferatoxin, cyclophosphamide, cisplatin, actinomycin D and 5-fluorouracil, 2-doxy-D-glucose, cholecystokinin octapeptide (CCK-8), lactose, morphine, oxycodone and ritonavir etc, to name a few (e.g., Alhadeff et al., 2015; Andrews and Horn, 2006; Aung et al., 2004, 2005; Batra and Schrott, 2011; De Jonghe and Horn, 2008; Doobay et al., 2021; Goineau and Castagné 2016; Horn et al., 2009, 2013; Krane et al., 1976; Kumar et al., 1983; Li et al., 2018; Limebeer and Parker, 2000; Liu et al., 2005; McCutcheon et al., 1992; Nakajima, 2018; Parker, 2014; Rudd et al., 1998; Shi, 2014; Shinpo et al., 2012; Takeda et al., 1993; Watson and Leitner, 1988; Watson et al., 1987; Wittlin and Brookshire, 1968; Yamamoto et al., 2002, 2004, 2007, 2011, 2014; Yuan et al., 2009) More compelling data supporting the strong link of pica-nausea/emesis can be further exemplified by the high resemblance of responses to cisplatin represented by the cancer patients and rats. Both species reacted to cisplatin with biphasic phases (acute and delayed) over time of drug action. (Andrews and Horn, 2006; De Jonghe and Horn, 2008). In addition, the widely known anti-emetics, such as 5-HT and NK1 receptor antagonists, suppressed pica in rodents (e.g., De Jonghe and Horn, 2008; Takeda et al., 1995a, 1995b); whereas growth differentiation factor 15 (GDF 15), a cytokine capable of inducing emesis in shrew (animal capable of vomiting), caused pica in rat (Borner et al., 2020). These similar neuropharmacological responses with rodents and emetic animals further suggested that rodent pica is highly correlated with nausea and emesis.

In 2012, a comprehensive meta-analysis of 311 publications on the topic of pica (Du Sert et al., 2012) concluded that "emetic and pica responses observed in the ferret and the rat, respectively, are predictive of the emetic liability in humans." In this work, it was found that the intensity of rodent pica response to ten emetic compounds was closely correlated with nausea/emesis responses in emetic species (including human, dog, and/or ferret), showing that the potency of drugs to induce the most robust emetic or pica responses were highly comparable between species (Du Sert et al., 2012).

While ample evidence suggests that pica is most likely the rodents'

equivalent of nausea/emesis in emetic animals, a few studies have questioned whether (1) pica is a reliable index for nausea/emesis; and, in relation to this, (2) whether it is suitable for drug screening studies dealing with routine nausea/emesis. To address the first issue, assaying both pica and nausea/emesis in a same species capable of vomiting seems a plausible strategy (e.g., Andrews and Horn, 2006). Two studies reported causative emotogens of rat pica induced merely emesis but no pica in *shrew* (Liu et al., 2005; Yamamoto et al., 2004). However, the following considerations should first be taken while analyzing data from *Suncus murinus*. First, the emetic shrew might be an inborn non-pica insectivore. Pica is not necessarily an inherent attribute in every species in whatever case of emetogen exposure (e.g., Krishnamani and Mahaney, 2000). Moreover, individual pica expression is contingent on physiological state that is amenable to multiple factors such as gender, developmental stage and living environment (e.g., Krishnamani and Mahaney, 2000; Pebsworth et al., 2019; Wakibara et al., 2001). As far as we know, there exists no sufficient literature reporting that *Suncus murinus* has the natural endowment of pica response. The foregoing shrews reportedly ingested a little amount of kaolin during habituation period (averaged less than ~ 1 g/daily) but not afterwards, a behavior similar to their control batch (Liu et al., 2005; Yamamoto et al., 2004). This may be explained by "neophagia" (acceptance of new and unusual foods) in the habituation period. From a teleological perspective, both vomiting and geophagy provide the organism with defense process against gastrointestinal toxicity or ailments during evolution (Horn, 2008; Krishnamani and Mahaney, 2000; Pebsworth et al., 2019; Zhong et al., 2021). Thus, it is reasonable to extrapolate that there is no need for shrew to detoxify emetogen via pica, while possessing the power to remove toxin through evolutionarily-developed emesis.

The second question stems from inconsistent responses, to some drugs, between pica reaction as shown by rats and nausea/emesis as demonstrated by emetic species (Andrews and Horn, 2006; Goineau and Castagné, 2016; Sanger et al., 2011; Zhong et al., 2021). For instance, apomorphine elicited no pica in rats (Takeda et al., 1993 and De Jonghe and Horn, 2008 reported the opposite) but was an emetogen for ferrets (Goineau and Castagné, 2016; Sanger et al., 2011). In addition, although cisplatin induced both rat pica and ferret emesis, this pica was resistant to the anti-emetic drug aprepitant which, however, effectually antagonized cisplatin-induced emesis in ferrets and dogs (Goineau and Castagné, 2016). These neuropharmacological discrepancies may suggest any or a combination of multilevel differences between species, including those in peripheral anatomy, gastrointestinal-associated molecules and neural substrates with regard to connectivity, membrane receptors and synaptic transmission (Goineau and Castagné, 2016; Horn et al., 2013; Sanger et al., 2011). In fact, no animal model can be applicable universally (Goineau and Castagné, 2016). While the rodent pica model cannot identify all emetogens or anti-emetic drugs, the unparalleled advantages that rodent model of nausea/emesis possess over other emetic species (see above) warrant its utility in combination with emetic animal model in drug screening during pre-clinic research (Du Sert et al., 2012).

Similarly, can the rodent pica model be applied to MS study? One primary task bearing on MS research is to unravel the neural machinery, from the perspective of circuits, cells and signal molecules, that drives or regulates MS development. In this case, pica only serves as gauge of MS attack which is triggered under the necessity of vestibular-activated pathways (upstream of DVC) that ultimately impact DVC (e. g., Arango et al., 1988; Balaban and Porter, 1998; Balaban, 2002; Belkacemi and Darmani, 2020; Catanzaro et al., 2014; Du Sert et al., 2012; Horn, 2008; Hornby, 2001; Koga et al., 1998; Napadow, 2013; Singh and Kuo, 2016; Yates et al., 1998; Zhang et al., 2017; Zhong et al., 2021) (Fig. 1). Many studies have documented the rodent pica response to vestibular challenges (see detailed discussion in the part "**3.1. Pica**"). By contrast, screening test in routine nausea/emesis study evaluates the drug's pharmacological and/or efficacious properties, as disclosed through drug's intervention in nausea/emesis-driving circuits (mainly downstream of DVC). It is these nausea/emesis-driving circuits that mainly account for the aforementioned emetogen-induced inconsistency between rodents and vomiting animals. Obviously, MS study (using pica merely as MS indicator) and chemo-induced (anti-)nausea/emesis research relate separately to their respective, causatively important sub-networks that are integral to the entirety of nausea/emesis-inducing network. Thus, the contextual difference-related species difference in pica response to emetogen suspectedly devaluing the validity of pica model of MS seem to be of no great concern.

2.3.2. CTAver and CTAvoi

Along with pica, CTAver and CTAvoi were likewise frequently used as alternatives indicating rodent nauseous/emetic condition (Andrews and Horn, 2006; Borner et al., 2020; Horn, 2008; Nakajima, 2018; Parker, 2003, 2014; Rinaman et al., 2009; Shinpo et al., 2012). Justification for CTAver's or CTAvoi's role as rodent nausea and/or emesis indicator(s) derives from a substantial number of studies that revealed the strong flavor/taste-gastrointestinal illness relationship, i.e., following conditioning, rodents consistently responded with CTAver or CTAvoi to many a stimulant known to cause human or emetic animals to vomit (see references as mentioned above).

Of note, in study of routine nausea/emesis, the term "CTAver" texted in a large body of literature actually referred to "CTAvoi" (Andrews and Horn, 2006; Lin et al., 2014; Parker, 2003; Schier et al., 2019). Although similar in literal sense and oftentimes used interchangeably, CTAver and CTAvoi describe two essentially different types of neural processes and behaviors in conditioned learning (Chambers, 2018; Davis and Riley, 2010; Mediavilla et al., 2005; Parker, 2003; Schier et al., 2019; Stafstrom-Davis et al., 2001). CTAver and CTAvoi do bear some resemblances. For instance, during conditioning both use novel flavored/tasted food/drink as conditioned stimulus (CS) paired with toxic substance exposure or aversive stimulation (unconditioned stimulus, US). Also, reduction in CS food/fluid intake features both CTAver and CTAvoi. Nevertheless, CTAver and CTAvoi differ in several aspects. First, foraging and consuming food for subsistence involves two phases: appetitive phase, i.e., goal-directed motor sequence involving food craving, seeking and contacting etc.; and consummatory phase, i.e., stereotypic oromotor reflexes mediating taste-driven food consumption involving ingestion or rejection (e. g., Lee et al., 2019; Parker, 2003, 2014; Schier et al., 2019). In cases of conditioning, the CTAver relates to consummatory phase, while CTAvoi to both appetitive and consummatory phases (e. g., Chambers, 2018; Jung et al., 2022; Lin et al., 2014; Parker, 2003; Schier et al., 2019). Second, rodents with CTAver show a hedonic shift (downshift of CS taste palatability), while CTAvoi shows no change in hedonic appeal (e.g., Jung et al., 2022; Lin et al., 2014; Schier et al., 2019). These can be discriminated by measuring CS palatability via an approach referred to as taste reactivity (TR) test. Testing TR provides quantitative readout on oromortor and somatic movements, including ingestive responses (such as rhythmic mouth movements, symmetric tongue protrusion, lateral tongue protrusion and paw licks, etc), and/or aversive responses (such as gaping or retching, chin rubbing, face washing, forelimb flailing, paw treading and head-shaking) to infusion of CS-tastant via intraorally implanted cannula (e. g., Jung et al., 2022; Lin et al., 2014; Parker, 2003; Schier et al., 2019). Third, CTAver and CTAvoi implicate differential neural processing of gustatory and US-interoceptive signal integration (CS-US interaction). For instance, CTAver is highly subject to influence of functional insular cortex, putamen and pallidum but not basal lateral complex of amygdala (BLA), while CTAvoi may necessitate both BLA and insular cortex for its normal expression (e.g., Jung et al., 2022; Parker, 2014; Reilly and Bornovalova, 2005). Finally, CTAvoi may possibly link with US of different nature. By decreasing intake of tastant to avoid CS-taste/flavor, CTAvoi links to an anticipated danger to "internal mileu", apart from nausea/emesis (e.g., Jung et al., 2022; Parker, 2014; Schier et al., 2019). This position is based on the fact that CTAvoi could be produced otherwise by non-nauseous US such as drugs of abuse (for instance,

morphine and amphetamine), pain stimulation (like footshock) and lactose (see reviews, Parker, 1995, 2003, 2014; Verendeev and Riley, 2012). In contrast, CTAver, by identifing taste disgusting (such behaviors as gaping and declining ingestive responses) through TR test, reflects gastrointestinal malaise (e.g., Jung et al., 2022, Lin et al., 2014; Schier et al., 2019).

It is obvious that since CTAvoi, unlike CTAver, does not necessarily implicate gastrointestinal malaise, much caution should be taken against misinterpretation of data on CTAvoi, especially when relating the flavored/tasted tastant to nausea/emesis if animals are conditioned with novelly patterned CS-US pair.

2.4. Pica and CTAver/CTAvoi as proxies for motion sickness

2.4.1. Pica

As putative analogue of nausea/emesis and, like CTAvoi, rodent pica was frequently applied to MS study (e.g., Idoux et al., 2018; Inprasit et al., 2018; Machuca-Márquez et al., 2021; McCaffrey, 1985; Mitchell et al., 1977b; Morita et al., 1988a, 1988b; Santucci et al., 2009; Sato et al., 2009; Takeda et al., 1986, 1995a, 1996; Zhang et al., 2022). Due to the close pica-nausea/emesis relationship (e. g., Mitchell et al., 1977a, 1977b; for more references, see above), use of pica is reasonably a more suitable way than others for identifying a pathological condition associated with rodent MS. Reportedly, indices such as piloerection, urinal and fecal incontinence, or hypothermia were also employed (Ngampramuan et al., 2014; Yu et al., 2007); nevertheless, these motion-induced responses may alternatively reflect prodromal autonomic distresses, set of signs preceding nausea/emesis associated with MS attack (Bertolini and Straumann, 2016; Brainard and Gresham, 2014; Leung and Hon, 2019; Money, 1970; Nalivaiko et al., 2014; Singh and Kuo, 2016; Yates et al., 2014).

Notably, there are inter-strain (e.g., Wistar vs Sprague-Dawley rats and C57/6 J vs Swiss CD-1 mice) and inter-individual differences in pica response. Also, rats or mice may exhibit temporal variation in pica during the test session (De Jonghe and Horn, 2008; Goineau and Castagné, 2016; Liu et al., 2005; Santucci et al., 2000; Takeda et al., 1993; Yamamoto et al., 2011; Zhang et al., 2022). Reportedly, Swiss CD-1 mice ingested kaolin, 1–7 g/day on average, but C57/6 J strains did not (Liu et al., 2005; Santucci et al., 2000). Furthermore, gender and age also figure significantly in pica to motion exposure. Following rotary stimulation, female consumed more kaolin than male; and pica was increased with development (Santucci et al., 2000, 2009).

When using pica to assess MS, several details need to be considered. (1) Stimulating paradigm of MS-inducement. Vestibular stimulation at constant velocity or acceleration usually caused no MS (Horii et al., 1993; Money, 1970). In human and shrew, incidence of MS is contingent on the movement oscillation magnitude and frequency, with human MS incidence being described by a curvilinear curve over the frequency spectrum (Diels and Howarth, 2013; Javid and Naylor, 1999; Leung and Hon, 2019; O'Hanlon and McCauley, 1974). Furthermore, the body orientation, which affects the alignment of vestibular labyrinth with the moving direction, is closely related to the MS sensitivity. Rat pica depended on the direction of stimulation, with sinusoidal linear acceleration along the rostro-caudal axis being most robust, followed by stimulation along the medio-lateral and dorso-ventral axes (Horii et al., 1993). Therefore, since a multitude of factors affect MS development, no pica in rats/mice after a 40 min-centrifuge rotation exposure might not reasonably argue against the utility of pica as rodent MS indicator; rather, it may be due to the ineffective stimulating paradigm (Yu et al., 2007). (2) Accuracy in kaolin measurement. Unlike human MS questionnaire or visually-based counts of retching/vomiting episodes (Yamamoto et al., 2004; Yu et al., 2007), pica measurement, by weighing the kaolin ingested by rats, has the advantage of being an unbiased and objective rating for MS severity. To ensure the reliability of pica and the subsequent true-to-fact evaluation of MS, it is critical to accurately measure the kaolin intake over a specified time epoch (per experiment design). All particles or crumbs of kaolin, including those with smallest size, littered on the floor of the cage must be collected, and the kaolin should be weighed to the nearest 0.01 g (e.g., Yamamoto et al., 2004; Zhang et al., 2022). (3) Inter-individual susceptibility difference. Variability in MS susceptibility exists between individuals and even the same subject shows different sensitivity to provoking motion (e.g., Golding, 2006). Therefore, in laboratory studies, to characterize the sensitivity of an individual rodent to a challenging motion, it was suggested to use the difference of kaolin intake between pre- and post-stimulation periods as the readout of motion response by the subject (Zhang et al., 2022). It is obvious that the absolute amount of post-stimulation kaolin intake, if adopted as independent variable either directly or with its normalized form (e.g., the ratio of absolute kaolin to the sum of kaolin/food intake) might definitely mask the inter-individual susceptibility (Zhang et al., 2022). (4) Delayed phase of pica. Interestingly, rat pica persisted at least four more days following an initial first-day response to cisplatin exposure (Yamamoto et al., 2014). Whether this behavior occurs similarly in case of MS is yet unknown, but deserves attention in the future work.

Noteworthily, the exact time span chosen for kaolin collection and measurement depends somewhat on the experimental objective in MS study. Consecutive hourly pica values helped to characterize the temporal profile of MS development (Mitchell et al., 1977a; Yamamoto et al., 2011, 2014), while one day or consecutive days of daily pica measurement over longer time block (e.g., 2- or ~ 24 h time length) were generally taken to appraise the effects of drug or neural interventions on MS (Inprasit et al., 2018; Mitchell et al., 1977a; Santucci et al., 2000; Yamamoto et al., 2014; Zhang et al., 2022). Reportedly, pica response was more robust nocturnally than at daytime (Yamamoto et al., 2011, 2014). Therefore, measuring nocturnal kaolin intake reasonably precludes the possible misinterpretation of MS experimental results, although diurnal (daytime) MS-induced pica also occurs (Santucci et al., 2009; Inprasit et al., 2018).

2.4.2. CTAver and CTAvoi

CTAver/CTAvoi can alternatively be chosen as indicator(s) of MS in rodents, in addition to their application in drug screening and pathological investigation relating to routine nausea/emesis (e. g., Chen et al., 2018; Deshetty et al., 2020; Gallo et al., 1999; Machuca-Márquez et al., 2021; Mitchell et al., 1977b; Wang et al., 2013, 2014). The majority of previous studies dealing with MS were conducted by assaying CTAvoi rather than CTAver, although oftentimes claiming to use "CTAver" test (Andrews and Horn, 2006; Lin et al., 2014; Parker, 2003; Schier et al., 2019). The surgical complexity and procedural difficulty associated with CTAver test might account for its extreme rarity as MS indicator. By contrast, CTAvoi is much simpler to perform, with rats and mice showing significant decrease in consumption of novel flavored solution of sugar, saccharin, or chocolate, etc (e.g., Andrews and Horn, 2006; Lin et al., 2014; Mitchell et al., 1977b; Parker, 2003, 2014).

3. Probing neurophysiology of motion sickness by using rodent models

Neural receptors mediating MS and chemo-induced nausea/emesis are different (Fig. 1). This can be understood intuitively and was also confirmed by experiments. Using rat pica model, diphenhydramine (a histamine-1 receptor competitive inhibitor) and ondansetron (5-HT3 receptor antagonist) were observed to selectively inhibit motion-induced pica and cisplatin-induced nausea/emesis, respectively, showing no cross actions (Takeda et al., 1995a, 1995b). In addition, vagotomy significantly affected lower dose of $CuSO_4$-induced (20 or 40 mg/kg, intragastric route), but no effect on motion-induced, emesis in musk shrew (Horn et al., 2014); and AP lesion in rats abolished CTAver induced by scopolamine methyl nitrate but enhanced motion-induced CTAver (Ossenkopp, 1983).

CTAvoi and pica rodent models are instrumental for unraveling the

neural mechanics underlying MS and for evaluating the efficacy of chemo-interventions in MS. For instance, pathways germane to MS development, such as the hypothalamus tuberomammilary histaminergic projections to brainstem, the histaminergic signaling and up-regulation of post-synaptic H1 receptor, were elucidated by using rodent pica model (Sato et al., 2009; Uno et al., 1997). Amygdala facilitation and hippocampal counteracting of MS were also revealed via rat pica model (Uno et al., 2000a). On the other hand, abolishment of MS upon blockade of histamine transmission at DVC via inactivating histamine N-methyltransferase (an histamine degrading enzyme), or via antagonism of H 1 receptor with promethazine (Chen et al., 2018), was observed using a rat CTAvoi model. A more recent study using mice CTAvoi showed that central vestibular glutamatergic CCK-neurons projecting to parabrachial nucleus conveyed the signal triggering MS (Machuca-Márquez et al., 2021). Finally, using a mouse pica model, it was observed that TRPV1-pPI$_3$K-pAKT-pCREB pathway in hypothalamus, thalamus and brainstem was activated upon MS attack; and the amount of both NGF in frontal cortex and hypothalamus and BDNF in hypothalamus were increased (Inprasit et al., 2018; Santucci et al., 2009).

4. Conclusion and future work

MS encompasses diverse symptoms (composing MS syndrome) that involve distribution of vestibular, visual and/or proprioceptive signals to neural circuits that mediate sensorimotor reflexes. Counter mearsures such as adaptation training and drug treatment have been proved useful in preventing or ameliorating MS. However, the complexity of MS, in terms of either its symptoms, types (such as car-/sea-/air-sickness, space MS and visually induced MS) or the causative inducements, makes fully understanding of MS no easy task. Many issues in this research field still remain to be further addressed, especially in an age when MS-inducible automated vehicle and virtual reality is becoming a trending popularity (Keshavarz and Golding, 2022). For instance, what is the exact etiology of MS? How the sensory inputs from vestibular, visual and proprioceptive inputs are processed (from circuitry, cell to molecular levels) in the brain to drive MS? In addition, although the classic drugs like antihistamines, anticholinergic agents and neuroleptics are effective in MS prevention, the accompanying notorious adverse effects (e.g., sedation) may greatly affect work performance (e. g., Schmäl, 2013). Therefore, new anti-MS drugs promising less side effects are still needed to be developed. In this context, application of animal models of MS which allow of invasive experimental approaches to dissecting neural mechanisms will undoubtedly provide valuable data for resolving the foregoing issues.

While rodent models are powerful tools for the study of MS, their use has been complicated by lack of vomiting reflex. This has led to questions regarding the validity of using rodents as model for MS, we present compelling evidence at circuit and behavioral levels that support rodent pica and CTAver/CTAvoi as proxies for the characteristic symptoms of MS, i.e. nausea/emesis. With low cost of maintenance, well-documented information on rodent behaviour and physiology, and diverse research tools applicable to rats/mice, rodent pica and CTAver/CTAvoi models will yield data complementary to those from emetic animal models (Goineau and Castagné, 2016), and will continue to contribute to understanding MS and development of new drugs (Borner et al., 2020; Inprasit et al., 2018; Machuca-Márquez et al., 2021).

Ethical statement

This review paper integrates and analyzes data on motion sickness from literature, involving no animal or human experiments.

CRediT authorship contribution statement

Fu-Xing Zhang, Ying-Shing Chan and Yun-Qing Li: conceptualization, original draft and editing, validation and supervision, and funding acquisition. **Xiao-Hang Xie, Zi-Xin Guo, Hao-Dong Wang and Hui Li:** literature curation, editing, review and validation. **Kenneth Lap Kei Wu:** original draft, review and editing, and validation.

Declaration of Competing Interest

none.

Acknowledgements

This work is supported by the National Natural Science Foundation of China (31871216, 81171279, and 81071105), the Natural Science Basic Research Program of Shaanxi Province (2018JM7029017) and the Innovation Capability Support Program of Shaanxi (2021TD-57).

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