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Suppression of lithium chloride-induced conditioned gaping (a model of nausea-induced behaviour) in rats (using the taste reactivity test) with metoclopramide is enhanced by cannabidiolic acid

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ABSTRACT

We aimed to determine the potential of various doses of metoclopramide (MCP, a dopamine antagonist) to reduce lithium chloride (LiCl)-induced conditioned gaping (a nausea-induced behaviour) in rats, using the taste reactivity test. We then evaluated whether an ineffective low dose of cannabidiolic acid (CBDA, 0.1 μg/kg, Rock and Parker, 2013), the potent acidic precursor of cannabidiol (CBD, a non-psychoactive component of cannabis) could enhance the anti-nausea effects of an ineffective low dose of MCP. MCP (3.0 mg/kg) reduced conditioned gaping responses. Coadministration of ineffective doses of MCP (0.3 mg/kg) and CBDA (0.1 μg/kg) enhanced the suppression of conditioned gaping, over that of either drug alone, without interfering with conditioned taste avoidance. MCP dose-dependently reduced nausea-induced conditioned gaping in rats. As well, the suppression of conditioned gaping was enhanced when ineffective doses of MCP and CBDA were coadministered. These data suggest that CBDA could be a powerful adjunct treatment to anti-emetic regimens for chemotherapy-induced nausea.
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1. Introduction

Chemotherapy-induced nausea and vomiting are the most distressing side effects experienced by cancer patients undergoing chemotherapy treatment, greatly impacting quality of life (Morran et al., 1979; Cohen et al., 2007; Naeim et al., 2008; Lohr, 2008; Hilarius et al., 2012). With pharmacological advances such at the introduction of the 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists (such as ondansetron, OND), control of chemotherapy-induced emesis in the clinic has been more successful than the suppression of nausea (Morrow et al., 1995, 1998; Gralla et al., 1999). Furthermore, although 5-HT$_3$ receptor antagonists are effective in reducing *acute* nausea and vomiting after chemotherapy, they are less helpful in managing *delayed* nausea and emesis (Morrow et al., 1995; Hsu, 2010).

Dopamine (DA) receptor antagonists, such as the dopamine$_2$ (D$_2$) receptor antagonist metoclopramide (MCP, Reglan) predate the currently prescribed 5-HT$_3$ antagonists. In the 1970–1980s, MCP was quite effective in managing cisplatin-induced emesis (e.g. Kris et al., 1983). With the advent of the 5-HT$_3$ receptor antagonists, the clinical use of DA antagonists has diminished; however, MCP is still used as a treatment for breakthrough chemotherapy-induced nausea and vomiting (occurring despite prophylactic treatments for which rescue anti-emetics are needed) and as an adjunct medication in an antiemetic regimen for refractory (occurring during subsequent chemotherapy cycles if antiemetic agents have failed in previous cycles) chemotherapy-induced nausea and vomiting (Lohr, 2008; Perwitasari et al., 2011). In fact, as outlined in the *Cleveland Clinic Protocol* for treating nausea and vomiting in advanced cancer, MCP is still the first recommended drug (Gupta et al., 2013). Side effects associated with the DA antagonist activity of MCP (occurring in 8% or less) are: extrapyramidal reactions, anxiety, hyperactivity and tremors (Fiore and Gralla, 1984; De Mulder et al., 1990).

Although the exact mechanism of action of MCP is unclear, it has been shown to directly affect the chemoreceptor trigger zone in the area postrema (vomiting centre of the brain) by blocking D$_2$ receptors (see Perwitasari et al., 2011), which may account for MCP's anti-emetic effect in chemotherapy patients (Harrington et al., 1983). However, only at high doses (2 mg/kg i.v. every 2 h, up to 10 mg/kg over 24 h) is MCP effective in the clinic at reducing cisplatin-induced emesis (Gralla et al., 1981). In contrast, high doses of other DA antagonists such as domperidone do not prevent cisplatin-induced emesis (Tonato et al., 1985; Saller et al., 1985). Therefore, it is likely that the high dose anti-emetic effects of MCP are not due to its action at the D$_2$ receptor because

Abbreviations: 5-HT, 5-hydroxytryptamine; 5-HT$_{1A}$, 5-hydroxytryptamine$_{1A}$; 5-HT$_3$, 5-hydroxytryptamine$_3$; CBD, cannabidiol; CBDA, cannabidiolic acid; D$_2$, dopamine$_2$; DA, dopamine; i.p., intraperitoneally; i.v., intravenously; LiCl, lithium chloride; MCP, metoclopramide; OND, ondansetron; SAL, saline; s.c., subcutaneously; VEH, vehicle.

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MCP (at high doses) has also been shown to be a 5-HT_3 receptor antagonist, like OND (Miner et al., 1987).

Animal models of emesis have evaluated the efficacy of MCP. MCP (ED_{50} = 0.16 mg/kg, subcutaneously, s.c.) in dogs has a fast (5 min) onset in reducing apomorphine-induced emesis (Niemegeers, 1982). In ferrets, MCP reduces morphine-induced vomiting episodes by 48% (at 3 mg/kg, intravenously, i.v.) and 82% (at 10 mg/kg, i.v.), having no effect on latency, while 0.1 and 1.0 mg/kg (i.v.) increases the latency to the onset of vomiting, but not the number of episodes (Wynn et al., 1993). In addition, in the ferret, MCP (2.24, 4.08 and 7.07 mg/kg, i.v.) significantly reduces cyclophosphamide-induced vomiting, as well as cisplatin-induced vomiting at 2 and 4 mg/kg, i.v. (Costall et al., 1986). However, MCP does not reduce prostaglandin E_2 - or naloxone-induced emesis in ferrets at 0.3 and 3 mg/kg s.c. and intraperitoneally (i.p.), respectively, nor does it reduce resiniferatoxin (a capsaicin analog that activates vanilloid receptors)-induced emesis (3–30 μmol/kg, s.c.) in ferrets. In *Suncus murinus* (house musk shrew), MCP (100 mg/kg, s.c. or ID_{50} = 410 μg/kg i.p.) suppresses cisplatin-induced emesis (Matsuki et al., 1988; Ito et al., 1995). These findings indicate that MCP may only be effective in managing emesis at higher doses that are indicative of its 5-HT_3 receptor antagonist action; an effect consistent with the human literature. Indeed, pretreatment with classic 5-HT_3 receptor antagonists reduces toxin-induced vomiting in *S. murinus* (Matsuki et al., 1988; Torii et al., 1991; Sam et al., 2003) and ferrets (Miner et al., 1987; Higgins et al., 1989; Rudd and Naylor, 1994; Nakayama et al., 2005), and in rats, OND interferes with conditioned gaping (Rudd et al., 1998; Limebeer and Parker, 2000; Tuerke et al., 2012a, 2012b) in the taste reactivity test (Grill and Norgren, 1978) elicited by a lithium chloride- (LiCl) paired flavour, a rodent model of nausea-induced behaviour (see Parker et al., 2008 for review). Unlike conditioned taste avoidance, which can be produced not only by emetic drugs, but also by rewarding drugs such as amphetamine, conditioned gaping is selectively elicited by drugs that produce vomiting in emetic species, such as shrews (Parker et al., 2003, 2008).

Evidence indicates that the non-psychoactive phytocannabinoid cannabidiol (CBD) effectively reduces nausea and vomiting in animal models. CBD reduces toxin-induced vomiting in *S. murinus* (Kwiatkowska et al., 2004; Parker et al., 2004; Rock et al., 2011, 2012) and reduces LiCl-induced conditioned gaping; effects that seem to be mediated by indirect 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) receptor agonism (Rock et al., 2011, 2012). Systemic administration of a 5-HT_{1A} receptor antagonist blocks CBD's reduction of vomiting in *S. murinus* and conditioned gaping in rats (Rock et al., 2012). The administration of CBD to the dorsal raphe nucleus, the site of somatodendritic 5-HT_{1A} autoreceptors, reduces the establishment of conditioned gaping and this central effect was blocked by systemic administration of WAY100635, the highly selective 5-HT_{1A} receptor antagonist (Rock et al., 2012). These results suggest that CBD may be exerting its anti-nausea properties by reducing forebrain 5-HT release, most likely in the visceral insular cortex (Tuerke et al., 2012a, 2012b).

Recent research from our group indicates that CBD's acidic precursor, cannabidiolic acid (CBDA, Potter et al., 2008) is about 1000 times more potent than CBD in reducing LiCl-induced emesis in *S. murinus* and conditioned gaping in rats (Bolognini et al., 2013; Rock and Parker, 2013) and, like CBD, CBDA's ability to suppress conditioned gaping and vomiting was blocked by pretreatment with the selective 5-HT_{1A} receptor antagonist, WAY100635. Most recently, we discovered that an ineffective dose (0.1 μg/kg, i.p.) of CBDA enhanced the suppressive effect of low doses of the 5-HT_3 receptor antagonist OND on LiCl-induced conditioned gaping (Rock and Parker, 2013).

1.1. Objective

The experiments presented here sought to examine the ability of various doses of the anti-emetic MCP (a D_2 receptor antagonist/5-HT_3 receptor antagonist) to reduce LiCl-induced conditioned gaping. We expected to see little to no suppression of conditioned gaping at the low dose of MCP, and significant gaping suppression at the highest dose of MCP, as both the animal and human emesis literatures suggest that higher doses, indicative of its 5-HT_3 receptor antagonist action, are effective. Additionally, we also evaluated the potential of a previously established ineffective low dose (0.1 μg/kg) of CBDA (Rock and Parker, 2013) to facilitate the anti-nausea effects of an ineffective dose of MCP. We hypothesized that coadministration of ineffective doses of CBDA would facilitate that anti-nausea effects of MCP, as was shown with CBDA and OND (Rock and Parker, 2013).

2. Materials and methods

2.1. Animals

Animal procedures complied with the Canadian Council on Animal Care. The protocols were approved by the Institutional Animal Care Committee, which is accredited by the Canadian Council on Animal Care. Male Sprague–Dawley rats (Experiment 1, n = 30; Experiment 2, n = 32), weighing between 278–352 g on the day of conditioning, obtained from Charles River Laboratories (St Constant, Quebec) were used in the experiments. They were single-housed in opaque plastic shoebox cages (48 × 26 × 20 cm), containing bed-o-cob bedding from Harlan Laboratories, Inc. (Mississauga, Ontario), a brown paper towel and Crink-l'Nest™ from The Andersons, Inc. (Maumee, Ohio). Additionally, in the home cage, rats were provided with a soft white plastic container that was 14 cm long and 12 cm in diameter. The colony room was kept at an ambient temperature of 21 °C with a 12/12 hour light–dark schedule (lights off at 8 am). The rats were maintained on food (Highland Rat Chow [8640]) and water ad-libitum.

2.2. Experimental procedures

2.2.1. Experiment 1: determination of potential of MCP to suppress LiCl-induced conditioned gaping

All rats were surgically implanted with an intraoral cannula under isofluorane anaesthesia, according to the procedures described by Limebeer et al. (2009). At least three days after the surgery, the rats received a TR adaptation trial in which they were placed in the taste reactivity chamber with their cannula attached to an infusion pump (Model KDS100, KD Scientific, Holliston, MA, USA) for fluid delivery. The taste reactivity chambers were made of clear Plexiglas (22.5 × 26 × 20 cm) that sat on a table with a clear glass top. A mirror beneath the chamber on a 45° angle facilitated viewing of the ventral surface of the rat to observe orofacial responses. Water was infused into their intraoral cannulae for 2 min at the rate of 1 ml/min.

On the day following the taste reactivity adaptation trial, the rats received a conditioning trial in which they were administered a pre-treatment injection of MCP (0.03, 0.3, 3.0 mg/kg) or SAL. Thirty minutes after the pretreatment injection, the rats were individually placed in the chamber and intraorally infused with 0.1% saccharin solution for 2 min at the rate of 1 ml/min while the orofacial responses were video recorded from a mirror at a 45° angle beneath the chambers, with the feed from the video camera (Sony DCR-HC48, Henry's Cameras, Waterloo, ON, Canada) with a fire wire connection into a computer. Immediately after the saccharin infusion, all rats were injected with 20 ml/kg of 0.15 M LiCl and returned to their home cage. The groups (with random assignment) were as follows: SAL (n = 7), 0.03 mg/kg MCP (n = 8), 0.3 mg/kg MCP (n = 8), and 3 mg/kg MCP (n = 7).

Seventy-two hours following the taste reactivity conditioning trial the rats were given the taste reactivity test trial, drug-free. Rats were again intraorally infused with 0.1% saccharin solution for 2 min at the rate of 1 ml/min while the orofacial responses were video recorded. Rats were then returned to their home cages. At 1600 h on the day of the taste reactivity test trial the rats were water restricted (water bottles removed from cage). Eighteen hours later on the following morning,

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