**Supplementary Table 2. The involvement of dopamine in mechanisms and symptoms of gastroparesis**

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| *Q1. What sources of dopamine could activate dopamine receptors in the AP?* |
| * In rodents, dopamine has been found within the AP, NTS, DMNV and in enteric neurons.1 * In humans, less is known. Dopamine is present within the human AP (detected 4-20h after death2), so could be released in response to an emetogenic stimulus. Neurons in the AP and adjacent NTS3,4 express many different receptors including the D2 and D3 receptors which when activated can cause vomiting.4,5 * It is a possibility that neurons within the AP could be activated by dopamine present in human blood, although ~98% of blood dopamine is conjugated to plasma proteins.6 Potential sources of endogenous dopamine include the postganglionic sympathetic neurons of mesenteric organs7,8 (noradrenergic neurons contain dopamine as a metabolic intermediate in the formation of noradrenaline), the adrenal medulla and from the GI tract (nM concentrations in human colon and gastric juice8), most likely from mucosal endocrine cells within the stomach, duodenum and colon9,8, gastric parietal cells (human, rat, mouse10,11) and perhaps from enteric neurons (rodents, possibly human12-16). * One example in which the occurrence of vomiting/ retching has been linked with an increased blood plasma concentration of dopamine (and adrenaline; free fractions for either monoamine were not determined) are patients with Riley-day syndrome experiencing a dysautonomic crisis17. * A theoretical possibility is that dopamine might be indirectly or directly increased within the AP via, respectively, vagal nerve activation to the adjacent NTS, or by endogenous emetic agents. |
| *Q2. What sources of dopamine might cause vomiting in gastroparesis?* |
| * Exogenously applied dopamine R-agonists cause vomiting.1 However, gastroparesis has yet to be associated with a rise of dopamine, or any other substance, in the blood capable of acting at the AP. * An unexplored possibility, at least in rats, is that the excitability of AP neurons is under rhythmic pacemaker-like control, via channels such as the hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channel.18 Disturbances in pacemaker activity, perhaps originating from changed gastric functions, could lead to release of dopamine within the AP via abdominal vagal afferent projections to the AP. In rats, apomorphine-induced conditioned taste aversion (a surrogate for nausea-like behaviour) may be inhibited by compounds blocking HCN channels.19 * In patients with intractable nausea, vomiting and hiccups (neuromyelitis optica spectrum disorder), enrichment of the aquaporin-4 water channel has been found within the AP.20 * Studies in mice show that stimulation of GI vagal sensory neurons can increase dopamine release in brain areas (*Substantia nigra*) involved in reward-seeking behaviours.21,22 However, the relationships between these findings and the symptoms of gastroparesis, if any, are unknown. |
| *Q3. Can dopamine cause nausea?* |
| * If D2 receptor agonists have *‘central anti-nausea effects’*23 the evidence and mechanisms of action are unclear. * In one study involving 33 gastroparesis patients in an emergency department, presenting with vomiting, were randomized to standard treatment with or without haloperidol or placebo.24 Those treated with haloperidol had lower scores for pain and nausea (5-point VAS). Broadly similar conclusions were reached in an uncontrolled open study on 52 patients.25 * Unlike domperidone, haloperidol can cross the blood-brain barrier and since D2 receptors are expressed by areas of the brain linked with nausea (eg., human insular cortex26) these findings could indicate a potential role for central D2 receptors in mechanisms of nausea. * In dog, intravenous dopamine induced retching/vomiting in <2min preceded by disrupted myoelectric activity in the antrum and small intestine (a potential ’nausea-like’ prodroma, although needs to be treated with caution); both effects were blocked by domperidone.27 |
| *Q4. How might endogenous dopamine slow gastric emptying during gastroparesis?* |
| 1. Dopamine acting directly on the stomach  * It has been suggested that a disease-specific release of dopamine could occur locally in the GI tract to inhibit gastric motility, but robust evidence is lacking.28 * In rodents, dopamine receptors are expressed within the GI tract.1 In guinea-pig and rat isolated stomach, domperidone increased stomach movements, reversed secretin-induced inhibition of motility (perfusion through celiac artery29,30) and improved coordination of gastro-duodenal waves of myogenic contraction (serosal addition31-33). * In some studies with isolated GI tissues*, exogenously applied* dopamine inhibited GI neuromuscular functions via D231,34-36 or D3 receptor activation37, but many similar studies were unable to identify a role for the D2 receptor in the functions of dopamine,38-48 includingwhen measuring myoelectrical activity.49 * In human isolated stomach, domperidone has no ability to mimic the actions of metoclopramide and other 5-HT4 receptor agonists to facilitate cholinergic activity.50,51 Together, these studies make it difficult to be confident that domperidone can increase gastric emptying by antagonising the actions of dopamine released within the stomach. Interestingly an intravenous infusion of dopamine increased plasma levels of motilin-immunoreactivity in humans52, although confusingly, a single oral dose of domperidone also increased motilin-immunoreactivity within the blood.53 As yet, there is no evidence for a role for endogenous motilin in the genesis of gastroparesis symptoms.  1. Dopamine acting within the brainstem  * Synaptic connections between the AP and the NTS54 suggests that D2 receptor antagonism within the AP could affect NTS activity, increasing vagal efferent activity to the stomach and increasing gastric emptying. In rats, it has been argued that the AP mediates the ability of apomorphine to inhibit and stimulate gastric movements54 and in the dog D2 receptors in the AP are implicated in the gastric relaxation induced by systemic apomorphine but not that produced by morphine suggesting a lack of involvement of peripheral D2 receptors in the relaxation56. |
| *Q5. Does domperidone (or other D2/D3 receptor antagonists) increase gastric emptying of solid meals?* |
| * Considering ‘solid’ meals only, small studies on healthy people have shown that single doses of domperidone did not increase gastric emptying of a test meal (400kcal; 13C-acetic acid breath test57) or a high-fat meal (13CO2 octanoic acid breath test58). * A small study in healthy volunteers suggest that domperidone can reduce gastric accommodation without changing gastric compliance and sensitivity (barostat study59) and was consistent with an earlier study in which air was introduced into the stomach of vagotomised patients.60 However, whereas the former hypothesised a link between food reward signalling in the brain and control of the gastric accommodation reflex (vagally-mediated), the earlier study might argue against this possibility. * Early studies with domperidone included several lacking control populations (e.g., treated with placebo). For example, a systematic review found most studies (18/28) showed improved symptoms, with increased gastric emptying in 9 of 15 studies, including those reported only as abstracts.61 However, only two of the positive studies published in full, contained placebo controls. In the first of these, in six diabetic gastroparesis patients, gastric emptying of a ‘solid’ meal was increased after acute dosing with domperidone.62 Similar findings were reported in a study on 12 patients dosed acutely but not after chronic administration (35-51 days).63 * A later systematic review64 on trials in patients with FD or GP found some ability of domperidone to increase gastric emptying (When considering all studies, change in GE T1/2 was not significant, but was significant when using optimal GE test methods (breath test or scintigraphy measured for 3 hours with solid meals) * The D2/D3 receptor antagonist trazpiroben did not affect gastric emptying (breath test) in patients with gastroparesis (interestingly metoclopramide was also without effects), although benefits in volume-to-fullness were seen.65 * In two small studies on patients with diabetic gastroparesis, gastric myoelectric dysrhythmia was said to be improved after long-term dosing without placebo control66 or in comparison with cisapride,67 each with improved symptoms. * Could domperidone increase gastric movements indirectly, by reducing nausea, early satiety and abdominal bloating?68 |

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