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Models and Assays for Evaluating Anti-Emetic Potential as well as Emetic Activity

Our studies evaluating emetic liability and testing potentially anti-emetic agents have primarily used ferrets and *Suncus murinus* (musk shrew). More information about the use of these models is shown below, along with examples of relevant publications.

More recently recordings of the electrogastrogram using radiotelemetry in ferrets [34, 48] and *Suncus murinus* [50] as well as mice have been used. Together with these, recordings of gastric slow waves using tissue sections on a microelectrode array platform have been used [68, 70, 72] to provide a new *in vitro* paradigm for investigating gastrointestinal function and anti-emetic activity in disease models. See below for a further description of this new paradigm.

Ferrets: Whole Body Plethysmography Chamber

- noise suppressed design
- temperature and humidity control probes.
- sensitive pressure transducer that measures pressure changes inside the chamber through air flow regulation.

Using the ferret, studies have looked at the mechanism of several drugs that cause emesis including apomorphine [1, 29], morphine [1, 5, 10], ipecacuanha [1, 39, 64], copper sulphate [1, 5, 14], chemotherapeutic agents [1, 8, 9, 15, 26], prostanoids [21, 32, 41, 43], and a range of peptides (e.g. exendin-4) [59, 65]. Other ferret studies on 5-HT_3 and NK_1 receptor antagonists have examined the anti-emetic potential of cannabinoids [52], dopamine receptor antagonists [1, 15, 32], opioids [5], peptides (e.g. exendin (9-39), ghrelin) [33], prostanoid receptor antagonists (unpublished), glucocorticoids [19, 36], ACTH analogs [26], monoamine reuptake inhibitors [39] and pungent and non-pungent vanilloids [42, 49, 53, 63].

Using *Suncus murinus,* studies have investigated the emetic properties of prostanoids [23, 25], chemotherapy [24] and the mechanisms of motion-induced emesis [17, 50]. The anti-emetic mechanism of action of opioids [18], NK_1 tachykinin receptor antagonists [17, 30], 5-HT_3 receptor antagonists and glucocorticoids [24], vanilloids [20], antitussive drugs [37], and anti-histamines [66] and peptides including exendin-(9-39)) [58], ghrelin [67, 69], and nesfatin [73] have also been investigated. This species has also been used to investigate mechanisms of drug- and chemotherapy-induced pica [27].

Techniques used in Emesis Research Projects

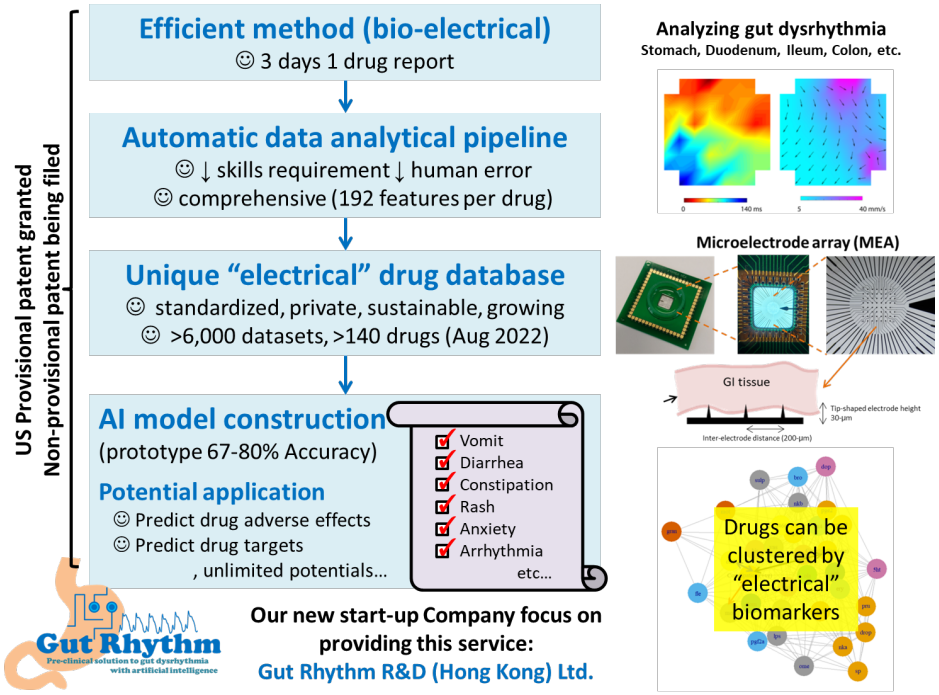
During experimentation, the following techniques/paradigms have been used:

- Examine pharmacology of drugs by oral, subcutaneous, intraperitoneal, intravenous, intraventricular, and intracerebral routes (see above for references)
- Define the potency of drugs on isolated tissues (e.g. ileum [35, 40]
- Evaluate drugs on mechanisms involved in the peristaltic reflex [31]
- Feeding experiments [57]
- Pica experiments [27]
- Microdialysis [45]
- Radiotelemetry [50]
- Measure glucose, insulin [55, 59]
- Use c-fos to investigate emetic pathways [58, 65]
- Investigate thermoregulation [60]
- Assess conditioned taste aversions [16]
- Lesion of abdominal vagi [23, 32, 41, 50]
- Lesion of the area postrema [44]
- Electrophysiological recordings from the isolated vagus nerve [28]
- Autoradiography [3-5]
- Heart rate variability studies [71]
- Assess cardiovascular function (radiotelemetry: BP, ECG,) [42, 53]
- Assess respiratory function (whole body plethysmography; [69, 72]

- Quantification of drug action on isolated tissues using the microelectrode array [38, 46, 47, 51, 54, 56]

A New Paradigm for Studying Gastric Dysfunction

Recording of electrical slow wave gastrointestinal pacemaker propagation activity has been used from isolated tissues for drug screening [68]. This proprietary protocol has been used to test >140 drugs on 4 types of tissues creating a novel Gastrointestinal Pacemaker Activity Drug Database (GIPADD). The current size of GIPADD allows >16 billion potential correlation tests to be calculated relative to clinical/preclinical data achieving 67-80% in predicting several drug adverse effects. The accuracy is expected to improve as new data sets are added. The unique slow wave electrical fingerprint of a new chemical entity is essentially matched to existing profiles in the database. This new approach to drug discovery is protected by a US patent. See https://gutrhythmrdhk.weebly.com for additional information.



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