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Translational studies of vasopressin in rat, ferret, shrew and human gastric antrum.

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Circulating levels of vasopressin are raised in association with nausea in humans whereas in rats exposed to nauseogenic stimuli, levels of oxytocin but not vasopressin are raised [Stern *et al* 2011]. Since rats do not possess the capacity to vomit it is common to use ferrets or the house musk shrew *Suncus murinus* instead. Here we compare the responses of stomach muscle strips taken from various mammalian species, including man, to vasopressin and oxytocin.

Human stomach was obtained at bariatric surgery for obesity following informed consent; animals were killed using schedule 1 methods. For the rat (*Rattus norvegicus*, Wistar strain, male, 160-225g, Charles River, U.K.) and shrew (*Suncus murinus*, male, 50-75g, St Georges, University of London, U.K.), stomachs were dissected out prior to strip preparation from the distal stomach (antrum) whilst for the ferret (*Mustella putorius furo*, Albino or Fitch (pigmented), male, 900-1850g, Merck, U.K.) distal stomach strips were prepared in situ. In the human stomach the mucosa was removed. All strips were cut parallel to the circular muscle and suspended in tissue baths for isometric recording (Kreb's; 5% CO_2 in O_2; 37°C; 0.5-2g tension). In the human stomach electrical field stimulation (EFS) was applied at 5Hz (0.5ms pulse width, 50V, 10s) every 1min, for sub-maximal responses. N = number of patients/animals. All drugs were added non-cumulatively.

Vasopressin caused an increase in stomach muscle tension in all species investigated. In human stomach this corresponded to an increase of 230±68 mg, EC_{50}=1.2nM, equivalent to 226±118% of the EFS-evoked contraction (100pM-100nM; n=1-4 each concentration). In the rat, shrew and ferret 100nM vasopressin caused a muscle contraction of 482±117 mg (a significantly greater increase than in other species, $P<0.05$; ANOVA plus Bonferroni post-test), 161±51 mg and 143±67 mg (n=6, 7, 6 respectively). In the ferret and shrew lower concentrations (2pM-1nM) were ineffective (n=5-8 each) whereas in the rat 1nM vasopressin caused a muscle contraction of 111±15mg (n=8). The Interestingly, oxytocin (100nM) also increased muscle tension in all species- in the human muscle tension was increased by 164±64 mg, corresponding to an increase of 41±11% EFS (n=3). In the rat 100nM oxytocin increased baseline muscle tension by 167±70 mg (n=6), in the shrew by 62±22 mg (n=6) and in the ferret by 690±463 mg (n=5). There was no significant difference in the responses to oxytocin between species. Vasopressin and oxytocin had little or no effect on the magnitude of EFS contractions in human stomach tissue (a small increase of 14±12% and 13±4% respectively was observed at 100nM; n=4, 3). For both vasopressin and oxytocin, the contraction persisted for >20 min in continued presence of the hormone for the human and rat (100nM, n=4, 6); in the ferret and shrew the response faded within 5 min (100nM, n=5-7 each).

Despite the many differences between the digestive systems of different laboratory mammalian species, comparative studies with humans are rare. Here we have shown that in humans, the effective concentrations of vasopressin are within the range induced by nausea. This indicates a potential direct role of vasopressin in inducing gastric dysrhythmias and perhaps, signalling the induction of nausea in humans. However, in other mammalian species the relative potencies of vasopressin and oxytocin change, suggesting different mechanisms by which these hormones might play a role in the mechanisms of nausea and emesis.

Stern, R. M., Koch, K. and Andrews P. L. R. (2011). Nausea, Mechanisms and management, Oxford University Press.