## THE EFFECT OF THE $NK_1$ RECEPTOR ANTAGONIST SR140333 ON CAPSAICIN-INDUCED PLASMA EXTRAVASATION (PE) IN THE MOUSE EAR.

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Capsaicin produces a dose dependent increase in PE in the mouse ear. We have tested the effect of the novel $NK_1$ receptor antagonist SR140333 (Sanofi, Montpellier) on the response to capsaicin in this model. Anaesthetised male mice (25-30g, LACA-Swiss, i.p. urethane) were injected i.v. with $^{125}$I-albumin as a marker of PE. Capsaicin ($3.3x10^{-7}$ moles in 20µl 100% ethanol) was applied to one ear and vehicle to the opposite ear. After 30min the animals were killed, the ears were removed, weighed and counted for radioactivity. PE is expressed as $\mu l \cdot g^{-1}$ of ear tissue. SR140333 ($1mgkg^{-1}$ i.p.) inhibited capsaicin induced oedema (165. 9±30.9, mean ±s.e.mean , n=6 vs 55.9±10.7, n=5, $p<0.01$, vehicle: 56.2 ± 13.9, n=5 ). The selectivity of SR140333 ($1mgkg^{-1}$) was tested in a skin oedema assay and inhibited the effects of the specific $NK_1$ agonist GR93632 (Glaxo, Ware) but not platelet activating factor (PAF) or histamine.

| | plasma extravasation (µl/skin site) | | | | |
|---|---|---|---|---|---|
| Agonist | vehicle | n | SR140333 | n | p |
| GR93632 (50pmol/site) | 4.7±0.5 | 9 | 2.4±0.3 | 10 | $p<0.05$ |
| PAF (1nmol/site) | 4.3±0.7 | 6 | 4.2±0.6 | 6 | ns |
| histamine (3nmol/site) | 3.2±1.2 | 7 | 3.6±0.5 | 6 | ns |

We conclude that increased vascular permeability induced by capsaicin in the mouse ear is primarily due to release of substance P which subsequently activates $NK_1$ receptors.

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## PATHWAYS OF SECRETION OF PROGASTRIN-DERIVED PEPTIDES IN TRANSFECTED GH3 CELLS.

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The segregation of secretory peptides to the regulated and constitutive pathways of secretion is incompletely understood. We have examined the sorting and processing of progastrin-derived peptides in transfected GH3 cells expressing wild type human progastrin, or a mutant in which the phosphorylation site is deleted ($Ser^{96}$ to $Ala^{96}$). Peptides were determined by RIA using antibodies specific for (a) progastrin but not its cleavage products, and (b) amidated gastrins *ie* G17 and G34. At 37°C there was linear secretion of both progastrin and amidated peptides. Brefeldin A (BFA), which inhibits transport of secretory proteins to, and beyond, the Golgi complex, and incubation at 22°C, which blocks exit from the *trans*-Golgi network, inhibited progastrin secretion, which is compatible with release via the constitutive route. A depolarizing stimulus (50mM KCl) increased release of amidated peptides, but not progastrin; neither BFA nor incubation at 22°C influenced the response to KCl, suggesting that amidated peptides were released from granules of the regulated pathway. The responses of cells expressing wild type and Ser-mutated progastrin were similar. **Conclusions.** 1, In transfected GH3 cells, amidated gastrins are generated in granules of the regulated pathway, and can be released by depolarization. 2, Progastrin is constitutively secreted. 3, The $Ser^{96}$ phosphorylation site is not obligatory for processing or segregation into the regulated pathway.