

## K4

### VIP/PACAP receptor regulation in a human sepsis model

Angela Storka<sup>1</sup>, Bernhard Burian<sup>2</sup>, Stefan Aschauer<sup>1</sup>, Breanna Clive<sup>1</sup> and Michael Wolzt<sup>1</sup>

<sup>1</sup>Department of Clinical Pharmacology, Medical University Vienna, 1090 Vienna, Austria

<sup>2</sup>Department of Pneumology, Medical University of Vienna, 1090 Vienna, Austria

E-mail: michael.wolzt@meduniwien.ac.at

### Background

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) act via three different G protein-coupled receptors (VPAC<sub>1</sub>, VPAC<sub>2</sub> and PAC<sub>1</sub>). The receptor-ligand interaction leads primarily to the activation of cAMP-dependent pathways. *In vitro* data and animal studies have shown that VIP and PACAP inhibit lipopolysaccharide (LPS)-induced pro-inflammatory responses, whereas the anti-inflammatory properties of VIP seem to be mediated preferentially through VPAC<sub>1</sub>. Emerging data, however, indicate that VPAC<sub>2</sub> may play an anti-inflammatory regulatory role. To investigate the role of receptor regulation in humans we have investigated the expression of VIP receptors in an endotoxin model.

### Methods

Venous blood from 56 healthy subjects (25 males and 31 females) was collected before, and 3, 7, and 24 hours after intravenous administration of *E. coli* LPS (2 ng/kg). In whole blood, monocytes were labelled and analyzed for VPAC<sub>1</sub>, VPAC<sub>2</sub> and PAC<sub>1</sub> by FACS to characterize receptor regulation. Fluorescence was normalized for monocyte cell count.

### Results

LPS administration caused a biphasic response of the receptors under study: At 3 h and 7 h, the number of receptors was significantly decreased from baseline.. At 24 h, the surface expression of VPAC<sub>1</sub>, VPAC<sub>2</sub> and PAC<sub>1</sub> was significantly increased. A median upregulation of VPAC<sub>1</sub> expression from 17% (range: 2–69%) to 35% (range: 2–87%), of VPAC<sub>2</sub> from 20% (range: 5–79%) to 43% (range: 4–86%) and of PAC<sub>1</sub> from 27% (range: 3–81%) to 40% (range 5–89%) was detected. Following systemic administration of *E. coli* LPS, a biphasic response of VPAC<sub>1</sub>, VPAC<sub>2</sub> and PAC<sub>1</sub> was noted. This result was consistent for all receptors studied.

### Conclusions

The evident difference between acute and delayed effects of LPS suggests that the upregulation of VIP/PACAP signalling pathways may play a role in chronic effects of inflammation.