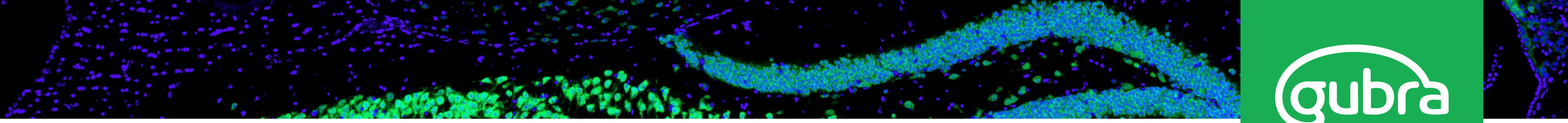

Whole Brain cFos Response to Different Amylin Receptor Agonists

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BACKGROUND & AIM

The pancreatic hormone amylin plays a central role in energy homeostasis by stimulating satiation and reducing food reward, making amylin receptor agonists attractive for treatment of metabolic diseases. Amylin receptors consist of heterodimerized complexes of the calcitonin receptor and receptor-activity modifying proteins subtype 1-3 (RAMP1-3). The current study aimed to map brain areas recruited by the different Amylin analogues (salmon Calcitonin, rat Amylin and Pramlintide).

Methods

The pancreatic hormone amylin plays a central role in energy homeostasis by stimulating satiation and reducing food reward, making amylin receptor agonists attractive for treatment of metabolic diseases. Amylin receptors consist of heterodimerized complexes of the calcitonin receptor and receptor-activity modifying proteins subtype 1-3 (RAMP1-3). The current study aimed to map brain areas recruited by the different Amylin analogues (salmon Calcitonin, rat Amylin and Pramlintide).

Results

All compounds resulted in a significant induction of cFos activation compared to the corresponding vehicle groups. Both sCalcitonin and rat Amylin activated numerous brain regions associated with appetite regulation (AP, NTS, PB and CEA). In contrast Pramlintide resulted in a more subtle cFos response and only the PB and CEA was activated.

1 High-throughput whole-brain 3D imaging pipeline

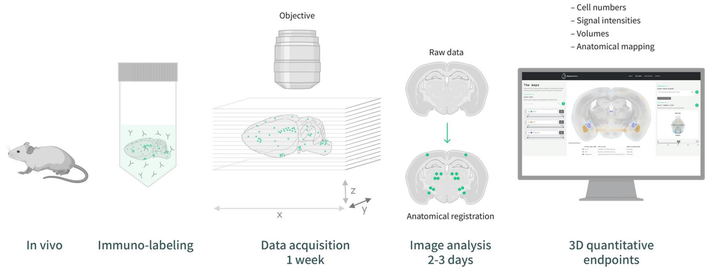

Figure 2. The workflow for generating cFos z-score maps maps. During the in vivo phase the mice were mock dosed for 4 days before being injected with compounds. The brains were stained for cFos, cleared and scanned with a light sheet microscope . The resulting data is mapped to a common coordinated framework (CCF).

2 Generation of digital brain maps

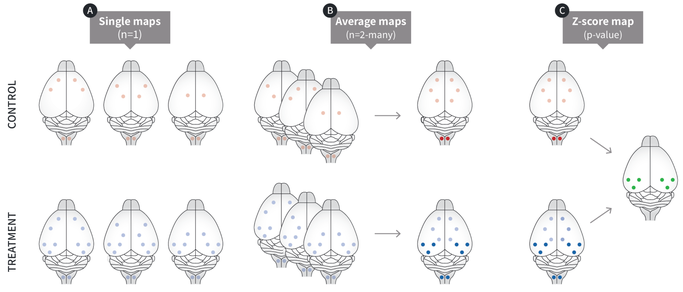

Figure 2. Generation of digital z-score maps. Z-score maps represents statistical differences between two groups at a voxel level. This allows maps from different studies to be compared to each other. In this study maps were generated from the studies. 1) Pramlintide and sCalcitonin, 2) rat_Amylin (WT) and rat_Amylin (RAMP1/3 KO) and 3) Fasted and Refed.

3 Z-score maps of different amylin treatments

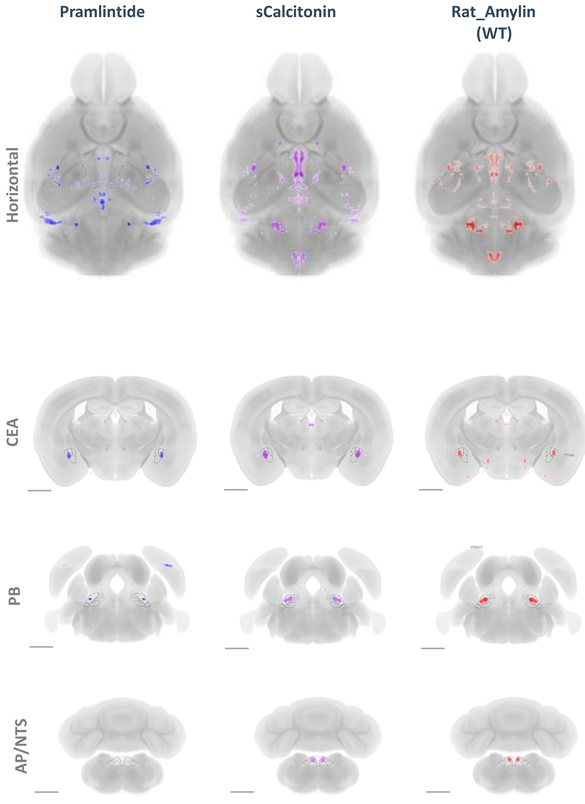

Figure 3. Z-score maps of drug induced neuronal activity. Treatment with different amylin receptor agonists resulted in differential neuronal activation. Treatment with Pramlintide resulted in activation in the CEA and PB, while sCalcitonin and rat amylin also activated neurons in the AP/NTS.

4 Comparison to other relevant maps

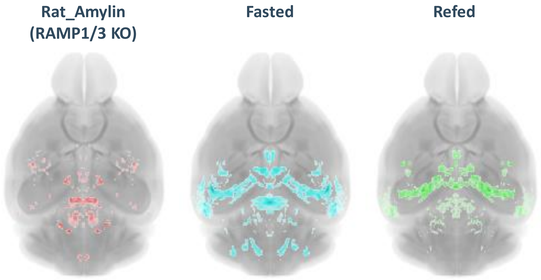

Figure 4. Z-score maps from other conditions. Using z-score maps it is possible to compare individual maps to other treatments. For examples it is possible to compare how rat Amylin activates neurons in mice lacking RAMP1/3 KO mice or how the maps compare to physiological conditions such as fasting and refeeding.

CONCLUSION

In conclusion, dosing with sCalcitonin and rat amylin resulted in strong cFos activation in both the brain stem (AP, NTS, LC and PB) and hypothalamic regions (BST and CEA). In contrast pramlintide only activated neurons in the PB and CEA.

All maps can be viewed in NeuroPedia. Scan barcode to access

www.neuropedia.dk

NeuroPedia