Helyes *et al.: Intrinsic Activity*, 2016; **4**(Suppl.3):A4.10
http://www.intrinsicactivity.org/2016/4/S3/A4.10
published online: 5 September 2016

INTRINSIC ACTIVITY

# 22nd Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the Hungarian Society for Experimental and Clinical Pharmacology

Vienna, 8–10 September 2016

*MEETING ABSTRACT*

## A4.10

### Somatostatin receptor subtype 4 ($sst_4$) regulates stress and depression-like behaviours in mouse models

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**Background:** Extensive evidence suggests a role of the inhibitory neuropeptide somatostatin released from a population of GABAergic interneurons in stress-regulation, anxiety and depression. However, very little information is available about its receptors ($sst_{1-5}$) mediating these effects. The $sst_4$ receptor is not involved in the endocrine actions of somatostatin, but it has potent anti-inflammatory and analgesic functions proposing drug development perspectives. Since it is expressed in several mood- and emotion-related brain areas, we investigated its role in stress regulation.

**Methods:** The role of the $sst_4$ receptor in the responses to acute and chronic stressors was examined with wild-type (*Sstr4*$^{+/+}$) and *Sstr4*-gene-deleted (*Sstr4*$^{-/-}$) mice, as well as with the selective agonist J-2156. Anxiety in acute stress situations was analysed in the elevated plus maze (EPM), while depression-like behaviour (immobility) was determined in the tail suspension (TST) and forced swim tests (FST). In a mild chronic variable stress (CVS) model, anhedonia was examined by the sucrose preference test (SPT), anxiety in the light–dark box test (LDB), while depression-like behaviour in the TST and FST. Endocrine responses to CVS were also investigated. Acute neuronal activation following TST was determined with Fos, while chronic neuronal activation in response to CVS with FosB immunohistochemistry in stress-related brain areas. Expression of $sst_4$ in the amygdala was detected using $sst_4^{LacZ}$ immunostaining in *Sstr4*$^{-/-}$ mice.

**Results:** Anxiety in the EPM and depression-like behaviour in the FST were significantly greater in *Sstr4*$^{-/-}$ mice compared to wild types. J-2156 exerted an anxiolytic effect in the EPM and an antidepressant-like action in the TST. J-2156 enhanced the TST-induced Fos response in several brain areas such as the central (CeA) and basolateral amygdala (BLA), which is supported by strong $sst_4^{LacZ}$ immunopositivity in these regions. *Sstr4*$^{-/-}$ mice showed greater susceptibility to mild CVS: it increased light preference in the LDB in wild-type mice, but not in *Sstr4*$^{-/-}$ ones. Immobility of *Sstr4*$^{-/-}$ mice in the TST increased after the CVS, and their greater baseline immobility compared to wild types decreased. However, anhedonia did not develop in this model and *Sstr4* deletion did not influence this parameter. CVS increased the adrenal weight to a greater extent in *Sstr4*$^{-/-}$ mice than in *Sstr4*$^{+/+}$ ones. The baseline plasma corticosterone concentration of *Sstr4*$^{-/-}$ animals was higher than in wild types, but it was not affected by the CVS. Expression of the chronic neuronal activation marker FosB increased in the CeA and BLA of *Sstr4*$^{-/-}$ mice following the CVS, but it did not change in these brain regions of wild types.

**Discussion:** These are the first data demonstrating that activation of the $sst_4$ receptor exerts anxiolytic and antidepressant-like effects in acute stress situations, as well as complex regulatory actions on chronic stress-induced behavioural and neuroendocrine alterations. The $sst_4$ receptor is present in the mouse CeA and BLA, where both its genetic deletion and selective activation influence acute and chronic neuronal responses to stress. These data suggest that $sst_4$ receptors in the amygdala play an important role in stress regulation.

**Acknowledgements:** This work was supported by the National Brain Research Program B KTIA_NAP_13-2014-0022 (ID: 888819).

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