

Meeting abstract

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## Neurokinin 1 receptor antagonism promotes active stress coping via enhanced septal 5-HT transmission

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Antagonists of the substance P (SP) preferring neurokinin 1 receptor (NK<sub>1</sub>-R) represent a promising novel class of drugs for the treatment of stress-related disorders including depression and anxiety disorders. The underlying neuronal mechanisms involved in the effects of these drugs, however, are poorly understood. By using *in vivo* microdialysis we observed increased SP, but reduced serotonin (5-HT) release during forced swim stress (FST) in the rat lateral septum (LS), a key area in processing emotions and stress responses. Acute administration of the selective high affinity NK<sub>1</sub>-R antagonist L-822429 injected either systemically or locally into the LS reversed the FST-induced decrease in 5-HT efflux and facilitated active coping strategies during the FST. Increased active coping in the FST was attenuated by intraseptal 5-HT<sub>1A</sub>-R blockade with WAY100635, indicating that the behavioural effect during NK<sub>1</sub>-R blockade is mediated by enhanced intraseptal serotonergic transmission acting on 5-HT<sub>1A</sub>-R. Taken together, our findings identify the LS as an important brain area for the modulation of stress responses by the SP/NK<sub>1</sub>-R system. NK<sub>1</sub>-R blockade resulted in behaviourally significant enhancement of 5-HT transmission. We show for the first time that this modulation does not necessarily involve interaction with neuronal firing at the cell body level of 5-HT neurons as previously postulated, but can be elicited in a terminal region of these neurons.