Antidepressant-like properties of the dual FAAH/TRPV1 blocker*N*-arachidonoylserotonin: role of the hypothalamic-pituitary-adrenal axis

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In recent years, several studies have explored the involvement of the deregulation of the hypothalamus-pituitary-adrenal (HPA) axis in the pathophysiology of depression. HPA hyperactivation as a consequence of acute/chronic stress has been found to play a major role in the neurobiological changes that are responsible for the instauration of depressive states (Bao et al., 2008; Pariante, 2003). Currently available medications present several limitations, including a time-lag for treatment response and low rates of efficacy. Recently, *N*-arachidonoylserotonin (AA-5-HT), a dual blocker at fatty acid amide hydrolase (FAAH) and transient receptor potential vanilloid type-1 channel (TRPV1), has been found to produce anxiolytic-like effects in mice (Micale et al., 2009). The present study was designed to assess the possible antidepressant-like properties of AA-5-HT under basal and stress conditions, in rats. To further investigate the possible involvement of the HPA axis and its eventual connections with the endocannabinoid system, we measured corticosterone levels in selected brain areas involved in the pathophysiology of depression (medial PFC and hippocampus) under basal, stress conditions, and in response to treatment with AA-5-HT. Our data show that the investigated compound has antidepressant-like properties in the forced swim test under stress conditions, and this effect is strictly connected with the normalization of the HPA axis deregulation that follows stress application. Blockade at FAAH/TRPV1 receptor may represent then a novel target to design new therapies for the treatment of depression and stress-related disorders.

Bao et al. (2008). *Brain research reviews* 57: 531-553
Pariante (2003). *Journal of neuroendocrinology* 15: 811-812.
Micale et al. (2009). *Neuropsychopharmacology* 34: 593-606.