



Substance P and Its Role in Anxiety Disorders

Riffat Mehboob^{1,2}¹Rotogen Biotech LLC, United States of America²Lahore Medical Research Center^{LLP}, Lahore, Pakistanriffat.pathol@gmail.com

ARTICLE INFO

How to Cite:

Mehboob, R. (2025). Substance P and Its Role in Anxiety Disorders: Substance P and Anxiety Disorders. *Pakistan Journal of Health Sciences*, 6(10), 01. <https://doi.org/10.54393/pjhs.v6i10.3576>

Anxiety disorders are the most prevalent mental illnesses in the world with an almost 19 percent prevalence among adults in the United States. Similar to major depressive disorder, they are associated with stress and pain and include disturbances in neurotransmitters like serotonin, dopamine, norepinephrine, and GABA and abnormalities in the activity of the amygdala and prefrontal cortex that leads to anxiety symptoms [1-3]. Exposure to stress results in increased endogenous Substance P (SP) in the central nervous system especially in the amygdala thus intensifying anxiety-related responses. This has led to a rising research interest on the role of SP in the development and control of anxiety disorders [4].

However, studies investigating psychiatric conditions often encounter methodological difficulties. Variables such as participant age, sex, and inclusion of subclinical populations can influence observed correlations and restrict the generalizability of findings. Moreover, findings of unexpected positive correlations between subclinical symptoms and gray matter volume challenge traditional interpretations, highlighting the importance of cautious analysis and interpretation of neuroimaging results [1,4].

Experimental evidence supports the involvement of SP in stress-induced anxiety. Animal studies have shown that emotional stress triggers SP release in the amygdala; for example, immobilization stress in rats leads to a prolonged elevation of SP in the medial amygdala (MeA), while mild stress causes only a short-lived increase. Notably, blocking neurokinin-1 receptors (NK-1R) in the MeA prevents the development of stress-induced anxiety-like behaviors, confirming the critical role of SP signaling in anxiety. Similarly, localized SP microinjections into specific brain regions have been shown to produce anxiogenic effects [4,5].

Moreover, SP triggers the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, leading to a high level of norepinephrine and cortisol, which accentuate the symptoms of anxiety even more. Simultaneously with the findings in MDD, NK-1R antagonists are shown to have anxiolytic effects thus supporting the primary place of the SP/NK-1R signaling in the pathophysiology of anxiety disorders [5].

REFERENCES

- [1] Besteher B, Gaser C, Nenadić I. Brain Structure and Subclinical Symptoms: A Dimensional Perspective of Psychopathology in the Depression and Anxiety Spectrum. *Neuropsychobiology*. 2020 Jul; 79(4-5): 270-83. doi: 10.1159/000501024.
- [2] Penedo JM, Rubel JA, Blättler L, Schmidt SJ, Stewart J, Egloff N et al. The Complex Interplay of Pain, Depression, And Anxiety Symptoms in Patients with Chronic Pain: A Network Approach. *The Clinical Journal of Pain*. 2020 Apr; 36(4): 249-59. doi: 10.1097/AJP.0000000000000797.
- [3] Remes O, Wainwright N, Surtees P, Lafortune L, Khaw KT, Brayne C. Generalised Anxiety Disorder and Hospital Admissions: Findings from a Large, Population Cohort Study. *BMJ Open*. 2018 Oct; 8(10): e018539. doi: 10.1136/bmjopen-2017-018539.
- [4] Ebner K, Rupniak NM, Saria A, Singewald N. Substance P In the Medial Amygdala: Emotional Stress-sensitive Release and Modulation of Anxiety-related Behavior in Rats. *Proceedings Of the National Academy of Sciences*. 2004 Mar; 101(12): 4280-5. doi: 10.1073/pnas.0400794101.
- [5] Ebner K and Singewald N. Substance P in Stress and Anxiety. In *Substance P*. Academic Press. 2025 Jan: 555-579. doi: 10.1016/B978-0-443-22194-1.00003-3.

