Early Life Stress Affects the Serotonergic System Underlying Emotional Regulation

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Traumatic events in early life are implicated in an increased risk of psychiatric diseases, such as depression and anxiety disorders. Serotonin is thought to play a central role in stress-induced psychiatric diseases. Serotonergic systems, including neural organization and receptor function, could dramatically change with each developmental stage. Here, we reviewed the persistent influence of early life stress on emotional regulation, focusing on the serotonergic system in rats. An aversive stimulus, foot shock (FS), during the early postnatal period (2–3 weeks after birth) produced behavioral, neuroanatomical and electrophysiological changes accompanied by serotonergic dysfunction, especially functional impairment of the serotonin (5-hydroxytryptamine; 5-HT)1A receptor in the cortico-limbic area. These findings suggest that normalization of the cortico-limbic serotonergic function has therapeutic potential for early stress-induced emotional disturbance.

Key words early life stress; serotonergic system; 5-HT1A receptor; psychiatric disease

1. INTRODUCTION

Traumatic events are implicated in an increased risk factor for psychiatric diseases. Especially, stressful “early life events” (infant/child abuse, neglect, or parental loss) could induce psychiatric disease, such as depression and anxiety disorder. In animal settings, physical and/or sensory stress during the early life stage induced depression-like or anxiety-like behaviors and learning impairment in adulthood. A common mechanism underlying stress-induced psychiatric diseases is thought to be the disruption of the serotonergic system in the central nervous system. For example, patients with depression showed low tryptophan (a precursor of serotonin) levels and were treated with selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs). Additionally, serotonergic projections to the limbic system are involved in the regulation of emotional stress. Here, we reviewed the persistent influence of early life stress on emotional regulation, focusing on the serotonergic system in rats.

2. DEVELOPMENT OF SEROTONERGIC SYSTEM

Two nuclei in the midbrain-pons, the dorsal raphe nucleus (DRN) and the median raphe nucleus (MRN), contain serotonin cell bodies (Fig. 1) that give rise to the majority of the serotonergic projections to the cortico-limbic system. Distinct projection areas of the DRN include the prefrontal cortex (PFC), lateral septum and amygdala, whereas the MRN innervates the medial septum, cingulate and dorsal hippocampus. These serotonergic projections from the DRN and MRN are involved in emotional regulation.

The developmental process of the serotonergic system is unique. Previous studies have revealed the serotonergic constitution in the forebrain during early postnatal periods. For example, in neonatal rats, transient and dense serotonergic innervation appears in all primary sensory areas of the cortex; however, these dense patches are not apparent at 3 weeks of age (3w). The serotonergic innervation becomes more uniform...
Shikanai et al. reported that in the rat DRN, the expression of serotonergic neurons containing, γ-aminobutyric acid (GABA) synthetic enzyme, which are involved in stress responses, transiently increases at 4 weeks of age (4w) and decreases thereafter. Developmental changes in the serotonergic system were also assessed by electrophysiological studies on neural activity in the PFC layer V pyramidal neurons. Serotonin induced a large depolarization followed by tonic firing at the age of postnatal day 14 (PD14 or, equally, postnatal 2w), whereas a small depolarization or hyperpolarization without cell firing was apparent at the age of PD21 (equally postnatal 3w). Thus, at postnatal 2–3 weeks, the serotonergic system could dramatically change with respect to neural organization and receptor function. These results indicate that the repertoire of neural activity precipitated by 5-HT could change depending on the developmental stage.

3. EFFECTS OF EARLY LIFE STRESS ON EMOTIONAL EXPRESSION

As described above, the early postnatal stage, in particular PD14 (2w)–PD21 (3w), is critical for the development of the serotonergic neural system, whereby proper behavioral responses to emotional stress may be established in adulthood. Indeed, we found that early life stress by exposure to an aversive stimulus, foot shock (FS) at the postnatal period of 2w or 3w (2wFS or 3wFS, respectively), produced behavioral abnormality and altered fear-related behaviors in adult male rats. For instance, conditioned fear-related freezing behavior was markedly attenuated during the retention period in 2wFS, and was enhanced in the extinction memory process during extinction trials and the extinction retrieval period in 3wFS, indicating impaired fear memory retention and extinction processes, respectively. In addition, anxiolytic behavior was noted in 3wFS under unconditioned fear stress. Histochemical findings revealed that the number of MRN serotonin-immunoreactive cells was remarkably reduced in 3wFS, as compared with control and 2wFS. These results suggest that early life adversity could cause persistent behavioral changes via the serotonergic neural system underlying emotional regulation.

4. EFFECTS OF EARLY LIFE STRESS ON SEROTONERGIC SYSTEM

The cortico-limbic area, such as the hippocampus and prefrontal cortex (PFC), are important regions for emotional regulation. Moreover, the synaptic efficacy among these brain regions is affected by sensory stress. Neural transmission in the hippocampal–PFC pathway, which is an efferent glutamatergic neuron, was attenuated by context-dependent fear memory, whereas was facilitated by anxiolytic drugs, diazepam or fluvoxamine. Furthermore, this neural circuit is modulated by serotonergic systems. Serotonin 5-HT1A receptor plays a key role in emotional regulation, and the 5-HT1A partial agonist tandospirone has been in clinical use for anxiety disorders. In animal settings, tandospirone attenuated fear memory retrieval, and facilitated extinction in the fear memory process via the PFC. Early life stress is also known to influence the serotonergic system. Maternal separation increased hippocampal 5-HT1A receptor expression. It was reported that 5-HT1A receptors located on the raphe nucleus were desensitized by maternal deprivation. We also revealed that 5-HT1A receptor function in the
hippocampal CA1 field was attenuated in 2wFS, but not in 3wFS. Moreover, early life stress attenuated 5-HT1A receptor function in the medial PFC (26, 27) (Fig. 3) and the dorsal hippocampus. The anxiolytic effects of tandospirone were decreased by early life stress, suggesting dysfunction of the 5-HT1A receptor. Thus, early life stress exerted prolonged influence on 5-HT1A receptor function, thereby possibly altering behavioral responses to emotional stress in adulthood.

5. CONCLUSION

This short review summarized the influence of early life stress on emotional regulation via serotonergic systems based on recent advances in our studies. Stressful events experienced during early life could precipitate long-lasting changes in neural circuits, and may lead to lifelong disturbances in emotional expression. Furthermore, 5-HT1A receptor dysfunction in the cortico-limbic area could be a key mechanism underlying behavioral abnormality elicited by early life stress. These findings may contribute to understanding the pathogenesis of psychiatric diseases, and suggest that normalization of serotonergic dysfunction in the cortico-limbic system has therapeutic potential for early life stress-induced emotional disturbances.

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