Endocannabinoid System

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Endocannabinoid System (ECS) is widely distributed in the central nervous system (CNS), constituting a complex signaling system that subserves multiple modes of synaptic transmission modulation. It is expressed at some synapses in all brain regions that are important for the processing of anxiety, fear and stress [1].

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1. Introduction

In cortical areas (including the cerebral cortex, hippocampus and cortical parts of the amygdala), CB1 receptor is expressed at higher level in cholecystokinin (CCK)-positive GABAergic interneurons, and at lower level in glutamatergic neurons. However, CB1 modulation in glutamatergic neurons has been shown to play an important role in the control of synaptic transmission and neuronal excitability [2][3]. The ECS represents, therefore, a negative synaptic feedback system activated by different neurotransmitters including glutamate, that acts to constrain neurotransmitter activity within stable and adaptive physiological ranges [4]. Since glutamate responses are not limited to synapse but continue into the nucleus where they promote cellular morphological remodeling, hence memory formation, another set of homeostatic mechanisms are devoted to buffer activity-dependent transcription through the rapid modulation of chromatin structure. This is mediated by transient modification of the level or activity of specific epigenetic modifiers [4][5][6].

Notwithstanding homeostatic mechanisms, environmental stress is always potentially toxic, as well as a prominent risk factor for psychiatric disorders [7]. Indeed, even if the majority of individuals can cope with stressful events neutralizing their harmful consequences, a substantial proportion of the human population cannot, being defined as vulnerable and developing long lasting signs of mental illness in response to trauma.

2. ECS and Epigenetic Homeostatic System Cross-Regulation

We recently documented that functional cooperativity between ECS and epigenetic homeostatic system is not limited to an outcome convergence toward limiting synaptic and neuroplastic effects of stress. In particular, a notable feedforward transcriptional mechanism orchestrated by LSD1 is aimed at reinforcing endocannabinoid-mediated suppression of stress-induced glutamate release in the hippocampus. As previously described, endocannabinoid 2-AG is synthesized in dendritic spines in response to glutamate via three main mechanisms of DAG lipase activation: one that is purely calcium-dependent, another that involves metabotropic Gq protein–coupled receptors, and a combined calcium assisted metabotropic mechanism [44]. In order to maintain correct levels of 2-AG concentrations, preventing unwanted inhibition of glutamate release and avoiding desensitization of CB1 receptor, this endocannabinoid is actively degraded by two hydrolases: post-synaptic ABHD6, and presynaptic MAG lipase (MAGL). In this frame, we suggested that in the hippocampus, peak 2-AG concentrations, required to counteract intense glutamatergic responses to social defeat stress are facilitated in mice by LSD1-mediated transcriptional repression of ABHD6 and MAGL [8].

LSD1, whose activity is transiently strengthened via stress-induced decreased levels of dominant negative isoform neuroLSD1, operates a negative modulation of ABHD6 and MAGL transcripts reflecting on protein availability within a homeostasis-demanding window of stress response [8]. Literature is concordant for what concerns 2-AG responses to acute stress, with many works reporting delayed (minutes to hours) 2-AG increase in the hippocampus, amygdala and prefrontal cortex as instrumental to neurotransmitter release regulation in these delayed windows of stress response [9][10][11]. Relevantly, 2-AG signaling in the hippocampus negatively regulates anxiety via positive modulation of DSE, but not inhibitory short-term plasticity [2], foreseeing a role for 2-AG increase as negative regulator of glutamatergic transmission. In general, hippocampal glutamatergic 2-AG signalling appears to be an essential component of adaptation to aversive situations [2].

LSD1-mediated repression of 2-AG degraders ABHD6 and MAGL probably cooperates with such an adaptation, contributing to increasing 2-AG tone in response to acute stress [8]. Indeed, stress-induced LSD1/neuroLSD1 ratio modulation in favor of LSD1 in the hippocampus occurs—requiring *de novo* transcription and functional modification of splicing factors—within hours. Although 2-AG has been shown to raise as early as half an hour after stress [9], LSD1 contribution to enhancing 2-AG levels via a posttranscriptional mechanism could be very relevant in situations of i) prolonged stress, ii) reiterated stress, iii) during the late phases of stress allostasis, all consistent with the duration of 2-AG increase in the same area.

Interestingly, not only LSD1/neuroLSD1 ratio modulation and raise of 2-AG concentration are compatible with their cross-regulation, but these molecular responses to stress also take place within a window characterized by decreased ability of memory formation. This temporary interval of hippocampal inhibition that follows a very limited moment of cognitive enhancement after immediate stress perception, features LTP unresponsiveness in the frame of a widely-accepted protective role against excitotoxicity [12]. This stress-operated hippocampal depression was initially interpreted as an unwanted maladaptive effect of the traumatic event [13], while more recently, such refractory window of memory-consolidation has been endowed with adaptive significance as a behavioral stress-coping strategy. The first inherent hypothesis was that temporary impairment of memory formation could be instrumental to writing, via inhibition of all other potential memories, a perfectly-shaped long-lasting aversive memory of the traumatic event [14][15]. Another possibility we would like to push forward is that this effect could instead hamper memory consolidation of the traumatic event *itself*, favoring stress resiliency via limiting the formation of a too-vivid and detailed internal image of trauma, which relevantly also represents a *core* PTSD symptom. Indeed, even if in the *immediate early* stress-response window, 2-AG increase seems to be important to improve memory formation mediating DSI and hence enhancing memory retention of inhibitory avoidance training [16][17](which is also consistent with the initial phase of cognitive enhancement [12]), in the delayed phase of stress response characterized by hippocampal inhibition—also featuring increased LTD probability likely with endocannabinoid contribution [18]— 2-AG could turn out to be necessary to DSE, contributing to temporary memory impairment or favoring extinction of the aversive memory instrumentally to resiliency [18]. For a graphical representation of biphasic 2-AG specificity see Figure 1. Thus, stress coping seems to display two opposing requirements the first being an immediate increase in cognition with protective purposes followed soon after, by the second requirement: to decreasing the quality of trauma-related memory traces (temporary memory impairment in Figure 1), again with the protective mean to limiting contextual anxiety arousal. Although biphasic 2-AG activity seems to be very likely it still requires a formal, comprehensive demonstration. A second relevant open question is whether LSD1-mediated MAGL and ABHD6 repression, functionally linked with increasing 2-AG [8] levels could be compatible with cognition enhancement or with a smemorizing effect. Considering the kinetic of LSD1-mediated MAGL and ABHD6 repression, which is delayed compared to initial stress perception, we suggest that LSD1 should be more functionally related with DSE promotion and more entrained with the window of hippocampal unresponsiveness. In this regard we can add that increased LSD1 activity is per se smemorizing [19] also displaying a prominent anxiolytic role in vivo [20].

3. Conclusions

There is no argument with regard to the physical and psychological stress-related nature of neuropsychiatric disorders. Yet, the mechanisms that facilitate disease onset starting from molecular stress responses are elusive. Environmental stress challenges individuals' equilibrium, enhancing homeostatic request in the attempt to steer down arousal-instrumental molecular pathways that underlie hypervigilance and anxiety. A relevant homeostatic pathway is the endocannabinoid system (ECS). In this entry, we summarize recent discoveries unambiguously listing ECS as a stress coping mechanism. We here emphasize a remarkable example of stress-coping network where transcriptional homeostasis subserves synaptic and behavioral adaptation, aiming at reducing psychiatric effects of traumatic experiences.

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