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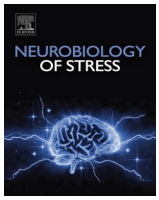

Brain receptor dynamics in early and adult life stress: Gateways to maladaptive coping strategies

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A B S T R A C T

Stress plays a significant role in the onset of numerous psychiatric disorders. Depending on individual resilience or stressor's nature, long-term changes to stress in the brain can lead to a wide range of behavioral symptoms, including social withdrawal, feelings of helplessness, and emotional overeating. The brain receptor molecules are key mediators of these processes, translating neuromodulatory signals into neuronal responses or circuit activity changes that ultimately shape behavioral outcomes. Here, I highlight several of my previous studies that reveal the pivotal role of receptor molecules in critical brain regions such as the nucleus accumbens, lateral hypothalamus, and lateral septum. I identified how mGluR5 signaling in the nucleus accumbens promotes stress resilience through pathways involving ΔFosB and SRF, while leptin receptor or glucocorticoid receptor signaling within lateral hypothalamic circuits contributes to stress eating. Additionally, I uncovered the role of dopamine receptor 3 signaling in the lateral septum in mediating the impact of early life stress on social behaviors. These findings underscore the functional relevance of brain receptor molecules in transducing stress—from early life through adulthood—into maladaptive coping behaviors. As druggable targets, these receptor-mediated pathways provide a critical foundation for developing targeted interventions to alleviate stress-related psychiatric symptoms.

1. Introduction

Over the past few decades, the neuroscience field has strived to understand the biological foundations of stress-induced psychiatric diseases. Since mood and emotional challenges are often seen as intangible or abstract, assessing the risk of mental illnesses largely relies on self-reports, which can be limited by an individual's reluctance to disclose their true feelings. The theory of "chemical imbalances" – the idea that a single neurotransmitter system (e.g., serotonin, dopamine) is primarily responsible for mental health conditions – raised awareness about mental health as a biological issue. However, given the profound complexity and heterogeneity of the brain, there has been a growing need for incorporating molecular, cellular, and circuit-level specificity in understanding the detrimental effects of stress on psychiatric symptoms.

Brain receptor molecules play a crucial role in mediating the brain's response to environmental stimuli, acting as frontline players in transducing signals of neurotransmitters, neuropeptides or hormones into intracellular actions, and activating complex signaling cascades that ultimately shape brain network functions. Unlike other molecular types, receptors in the brain are intricately regulated in their density, sensitivity, or localization through epigenetic modification, post-translational changes, or cellular trafficking, respectively. This dynamic regulation makes them particularly sensitive to environmental stress and stress hormones, which can promote maladaptive coping strategies in response to stress.

Notably, these brain receptor molecules are highly "druggable", making them attractive therapeutic targets in brain regions associated with emotional regulation, cognition, and social behaviors (Di Filippo et al., 2023; Hauser et al., 2017). Understanding how receptor molecules mediate the brain's stress response and how they can be leveraged to modulate neuronal activity, synaptic plasticity, and gene expression holds significant promise for developing targeted treatments for stress-induced psychiatric disorders. This review highlights progress in this field.

2. Stress in adulthood

Behavioral testing serves as a primary tool to measure the emotional states of laboratory animals, which are often interpreted as analogous to human psychiatric symptoms. However, repeated failures to translate animal behavioral test results into human outcomes – largely due to

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fundamental gaps between two species – highlight the importance of designing animal behavioral tests with high ecological and ethological validity to enhance their translational relevance (Gencturk and Unal, 2024; Shemesh and Chen, 2023).

My previous two studies (Shin et al., 2015; You et al., 2023) investigated behavioral stress responses in adult animal, employing experimental designs that incorporated etiological factors associated with behavioral abnormalities. These studies revealed how metabotropic glutamate receptor subtype 5 (mGluR5) and glucocorticoid receptors (GR) interact with chronic stress or threat stimuli to regulate stress resilience level and emotional overeating, respectively.

2.1. Accumbal mGluR5 in modulating stress resilience

Stress resilience is the ability to recover from trauma, threat, and deprivation, allowing one to maintain psychological well-being even after these adverse experiences (Feder et al., 2009; Russo et al., 2012). As experiencing stress is unavoidable in our daily life, understanding the neural mechanisms of resilience is crucial for developing preventive strategies and interventions for stress-induced psychiatric disorders. Recent studies have addressed the genetic, epigenetic and neural mechanisms of resilience, examining the roles of hormones, neuromodulators, and neurotrophic factors (Franklin et al., 2012); however, brain receptor molecules as key regulators of resilience remain understudied.

The 2015 study by Shin et al. (2015) identified mGluR5 (Kim, et al., 2008; Niswender and Conn, 2010) as a resilience-promoting brain receptor. Unlike other immediate early genes (IEGs), ΔFosB is unique because of its unusual protein stability. In the nucleus accumbens (NAc), for instance, exposure to chronic social defeat stress (CSDS) – a paradigm in which a mouse repeatedly experiences social subordination by an aggressive conspecific (Blanchard et al., 2001) – leads to sustained ΔFosB expression. This increased ΔFosB in the NAc has been shown to be both sufficient and necessary to prevent CSDS-induced social avoidance (Perrotti et al., 2004; Vialou et al., 2010), suggesting that elevated ΔFosB levels in the NAc promote resilience to chronic stress. Notably, Shin et al. (2015) suggested that mGluR5 in the NAc shell plays a key role in linking chronic stress to ΔFosB induction.

This study provided critical insights for several reasons. First, to examine depression-like behaviors in mice (depressive behavior hereafter) (Keifer and Summers, 2016), the authors employed three different behavioral paradigms of stress-induced depression (e.g., learned helplessness, restraint stress-induced anhedonia, and social avoidance after defeat stress). Unlike single-session anti-depressant screening tests such as the forced swim test (FST) and the tail suspension test (TST), these stress-based animal models consist of two independent phases: induction phase (i.e., stress exposure) and the testing phase (i.e., behavioral readout). Notably, a time interval between these two phases is designed to provide sufficient time for cellular or circuit-level changes to occur, allowing the development of stress resilience. Given the known association between independent stressful events and depressive episodes in humans, this behavior experimental design in the Shin et al. study better mirrors the etiological factors implicated in human depression, possibly increasing the translational value.

Second, in contrast to previous studies showing inconsistent results regarding the role of mGluR5 in depressive behaviors – primarily due to less reliable metrics in the single-session tests such as the FST and the TST (Deschwanden et al., 2011; Kovačević et al., 2012; Li et al., 2006; Tatarczyńska et al., 2001) – the Shin et al. study demonstrated consistent findings. Specifically, mGluR5 global knockout (mGluR5−/−) mice showed enhanced vulnerability to stress-induced depression across all three paradigms: learned helplessness, restraint stress-induced anhedonia, and social avoidance after defeat stress. Notably, the role of mGluR5 in promoting stress resilience became evident under an experimental design that allowed sufficient time for stressed mice to induce certain genes potentially required for the development of resilience. Again, this approach highlighted the importance of stress-based behavioral tests for studying resilience, providing a more reliable framework for investigating its underlying mechanisms.

Third, to identify specific brain regions that are responsible for the depressive behaviors of mGluR5−/− mice, the authors tested whether lentiviral rescue of mGluR5 in the NAc shell or core can reduce the behavioral phenotypes of mGluR5−/− mice. The results revealed that rescue of mGluR5 in the NAc shell of mGluR5−/− mice mitigated both social defeat-induced social avoidance and restraint stress-elicited anhedonia, whereas the same viral-induced mGluR5 expression in the NAc core did not. In addition, the authors found that wild-type control mice showed a substantial induction of ΔFosB in the NAc shell in response to chronic social defeat stress, but impaired ΔFosB induction was observed in mGluR5−/− mice under the same condition. This suggests that mGluR5 activity is required to enhance stress resilience via ΔFosB induction in the NAc shell.

Lastly, serum response factor (SRF) has been proposed as an upstream regulator of ΔFosB induction (Vialou et al., 2010). Notably, mGluR5 appears to regulate SRF activity via phosphorylation (pho-SRF), as evidenced by the finding that chronic social defeat stress increased pho-SRF levels in the NAc shell of wild-type mice but not mGluR5−/− mice. Furthermore, a local infusion of mGluR5 agonist (RS)-2-chloro-5-hydroxyphenylglycine (CHPG) into the NAc shell increased pho-SRF, accompanied by a sustained induction of ΔFosB. These data indicate that the mGluR5-SRF-ΔFosB signaling cascade in the NAc shell is a critical mechanism for promoting resilience in response to chronic stress. This discovery holds therapeutic potential, as targeting mGluR5—a brain receptor molecule—could pave the way for developing strategies that enhance resilience by driving cellular ΔFosB induction. Taken together, the Shin et al. study (Shin et al., 2015) found that mGluR5 activity in the NAc shell is necessary and sufficient for the development of stress resilience. The mGluR5 activity in the NAc shell is tightly linked to the activation of the SRF-ΔFosB signaling cascade, ultimately protecting against stress-induced depressive behaviors.

It is important to note that, upon repeated drug exposure, ΔFosB accumulation in the NAc has been implicated in the development of drug addiction, a maladaptive state. This suggests that ΔFosB may exert context-specific effects, promoting resilience under chronic stress conditions while facilitating the pathology of drug addiction after chronic drug exposure. Given the pivotal role of dopaminergic signaling in the NAc in modulating reward and motivation, future studies exploring the potential crosstalk between dopamine receptor signaling and mGluR5-SRF-ΔFosB activity in the NAc shell could provide valuable insights. Investigating how this interaction contributes to the differential processes observed under chronic stress vs. repeated drug exposure may deepen our understanding of the context-specific roles of ΔFosB.

2.2. Lateral hypothalamic GR in stress eating

Emotional eating refers to an increased tendency to overeat in response to negative emotions in the absence of physical hunger. For individuals exposed to life-threatening events in uncontrollable environments, emotional eating can provide relief from distress because it helps individuals to soothe the negative emotions associated with a loss of control (Tanofsky-Kraff et al., 2007; Yau and Potenza, 2013). Indeed, emotional eating can be a symptom of several serious mental illnesses, including depression, bulimia, and binge eating disorder, yet the pathophysiology of abnormal eating habits induced by stress has not been fully understood at the brain circuit level.

The lateral hypothalamus (LH) comprises a large portion of the hypothalamus, a key brain region involved in feeding, and contains several genetically distinct cell populations (Stuber and Wise, 2016). Proenkephalin (Penk) – a precursor of the endogenous opioid peptides met- and leu-enkephalin (Cadet et al., 2016; Castro et al., 2021) – is highly expressed in the LH, implicating that Penk-related neuropeptidergic systems in the LH may control physiological and emotional processes of

eating behaviors.

In the 2023 study by You et al. (2023), the authors identified Penk-expressing LH (LH Penk) neurons as a key subpopulation that plays a critical role in predatory threat stress (e.g., cat odor)-induced high-fat diet (HFD) overconsumption. Anatomically, the LH Penk neurons seem to be distinct from other relevant LH neuronal subsets that express pro-melanin concentrating hormone, hypocretin, or LepR. Using *in vivo* calcium imaging, the authors found that mice exposed to predatory scent stress (PSS) showed potentiated LH Penk neuronal reactivity to HFD consumption, whereas the same neurons in mice with no PSS history exhibited only a mild increase. This suggests that the PSS experience is a critical prerequisite for the emergence of HFD-salience-encoding activity in the LH Penk neurons. Furthermore, the authors found that chemogenetic activation of LH Penk neurons of normal control mice increased HFD intake, while the inhibition of the same population normalized the PSS-induced HFD overconsumption and aversive emotional states, supporting the idea that the activity of LH Penk neurons is critical for inducing the tendency toward emotional overeating observed in PSS mice.

The study also elucidated how the hypothalamic-pituitary-adrenal (HPA) axis, a principal neuroendocrine mechanism of stress (Chakraborty et al., 2020; Elzinga et al., 2003), orchestrates appetite regulation after PSS. Following PSS exposure, mice exhibited elevated serum corticosterone (CORT) levels, a hallmark of HPA axis activation. Notably, systemic pretreatment with CORT was sufficient to enhance LH Penk neuronal reactivity at the onset of HFD eating, mimicking the neuronal maladaptation observed in PSS mice. *In situ* hybridization data revealed that most LH Penk neurons express glucocorticoid receptors (GR) (Wong and Herbert, 2005), rendering them responsive to CORT. Inhibition of GR signaling in the LH effectively blocked PSS-induced HFD overconsumption and prevented heightened *in vivo* LH Penk neuronal activity during HFD intake. These results suggest that LH Penk neurons mediate predatory threat-induced HFD overconsumption through interactions with the stress hormone, CORT.

These findings provide an important framework that explains how the neuroendocrine system communicates with LH opioidergic circuits to drive emotional overeating after life-threatening events. It is important to note that the HPA axis is crucial in the time-dependent regulation of appetite after stress. Immediately after a stressor, corticotropin-releasing hormone (CRH), released at the apex of the HPA axis, suppresses food-seeking behaviors, prioritizing survival actions like escape or defense (Heinrichs and Richard, 1999; Richard et al., 2002). However, hours to days after a stressful event, glucocorticoids, the end product of the HPA axis, stimulate appetite and promote comfort eating.

Future research is necessary to uncover the CORT-mediated cellular/synaptic mechanisms underlying delayed-onset emotional overeating after PSS exposure. Given previous studies showing CORT-induced changes in synaptic transmissions, it is plausible that CORT-mediated delayed genomic processes — potentially involving GR-mediated transcriptional regulation —could influence AMPA receptor trafficking in LH Penk neurons (Krugers and Hoogenraad, 2009; Panettieri et al., 2019). Functional studies employing *in vivo* animal models will be essential to confirm this hypothesis.

3. Stress in early life

Exposure to early life stress (ELS) in the form of child abuse and/or neglect is associated with an increased risk of developing multiple behavioral dysfunctions in adulthood as a major symptom of psychiatric diseases (Heim and Nemeroff, 2001; Kessler et al., 1997). Previous clinical studies showed that major depressive disorder (MDD) patients with a history of ELS exhibited poorer response and remission rates to currently used antidepressants (Bruce et al., 2012; Nanni et al., 2012). Thus, the identification of such a distinct biological endophenotype of individuals exposed to ELS and specific neural mechanisms that transduce ELS into maladaptive behavioral patterns will provide greater insight into the development of novel therapeutic strategies.

In my previous work, two different versions of the maternal separation procedure were employed to replicate the ELS: early social deprivation (ESD) and early life trauma (ELT) paradigm. These approaches differ in the duration and nature of the separation: in the ESD paradigm, each pup was isolated from their mother and littermates for 3 h each day during the first two weeks of postnatal life (P1–P14), while the ELT paradigm involved a single 23-h isolation of 3-day-old mouse pups. Notably, these paradigms had differential long-term impacts: ESD primarily disrupted social behaviors, while ELT significantly affected eating behaviors in adulthood.

This distinction in the impact of ELS on various behavioral domains underscores the complex and multifaceted nature of early adversity. While social dysfunction is a well-documented outcome of ELS (Bandelow et al., 2004), the spectrum of effects also extends to cognitive impairments, emotional dysregulation, and changes in reward processing (Y. Chen and Baram, 2015; Novick et al., 2018), all of which contribute to the heightened susceptibility to psychiatric disorders in adulthood. Additionally, disruptions in metabolic and eating behaviors have been increasingly recognized as critical components of stress-related disorders, influencing the development of binge eating disorder, obesity, and metabolic dysfunction (Torres and Nowson, 2007). Therefore, investigation into the specific neural pathways that mediate these divergent effects of ELS is essential for advancing our understanding of how early adversities shape lifelong health outcomes.

3.1. Septal Drd3 signaling in ESD-induced social deficits

Dopamine receptor 3 (Drd3), a member of the D2-like receptor family, has been implicated in social deficits observed in psychiatric disorders such as autism spectrum disorder (ASD) (Staal et al., 2012). In the 2018 study by Shin et al. (2018), the ESD paradigm described above was used to investigate the effects of early life stress on Drd3 signaling in the lateral septum (LS). The study found that Drd3 signaling in the lateral septum (LS) is significantly downregulated in mice exposed to ESD. This molecular alteration is associated with pronounced social deficits, including impaired sociability in the three-chamber test and reduced ultrasonic vocalizations during social interaction. Using *in vivo* calcium imaging experiments, Shin et al. found that social stimuli significantly increase the activity of LS neurons expressing Drd3 (LS Drd3) in control animals but not in ESD mice. *Ex vivo* electrophysiology studies revealed that this reduction of LS Drd3 neuronal activity is likely due to a specific increase in the strength of the inhibitory inputs to these neurons. In addition, Kir2.1-mediated silencing of LS Drd3 neuronal activity mimicked the social impairments shown in ESD mice, while optogenetic activation of the same neurons ameliorated the ESD-induced social deficits. These findings establish that the activity of LS Drd3 neurons is, therefore, both sufficient and necessary for ESD-elicited social dysfunction.

Furthermore, the authors demonstrated that treatment with the Drd3 agonist PD128907 suppresses inhibitory synaptic inputs to the LS, thereby enhancing the LS Drd3 neuronal activity – a hallmark of normal sociability. Behaviorally, systemic administration of PD128907 could correct abnormal social behaviors of adult ESD mice, whereas chronic administration of fluoxetine, a commonly prescribed antidepressant, failed to alleviate ESD-induced social deficits. These findings suggest that individuals with a history of ELS may possess a distinct endophenotype that necessitates alternative therapeutic strategies beyond conventional treatments. Importantly, Shin et al. also showed that the beneficial effects of pharmacological activation of Drd3 signaling are not limited to ESD-exposed mice but extended to the BTBR strain of mice, a widely used model of ASD (McFarlane et al., 2008). These results underscore the critical role of Drd3 signaling in a broad spectrum of social dysfunction and highlight its potential as a therapeutic target for addressing social deficits associated with ASD and ELS.

Overall, this study highlights that ELS-induced downregulation in

Drd3 signaling and its corresponding effects on neural activity in the LS are critical to causing abnormal social behaviors. These findings pave the way for several avenues of future research. First, LS Drd3 neurons have dense reciprocal connections with the medial preoptic area (MPA) and anterior hypothalamic area (AHA), both of which are crucial nodes for various social behaviors (Ferris et al., 1997; McHenry et al., 2017). Future studies examining whether LS-MPA and/or LS-AHA circuit activity override predisposition to ESD-induced social dysfunction will expand our understanding of how the cell-type- and projection-specific circuits in the LS mediate social dysfunction caused by ELS.

Second, the authors demonstrated that activation of Drd3 signaling in the LS modulates synaptic transmission and *in vivo* neuronal activity, but the underlying mechanisms that couple Drd3 to intracellular signal transduction systems in the LS still need to be well defined *in vivo*. As a member of the D2-like receptor family, Drd3 primarily signals through the Gi protein pathway, which inhibits adenylate cyclase and reduces the levels of cyclic AMP, thus lowering protein kinase A (PKA) activity (Speranza et al., 2021). Intriguingly, prior studies raised the possibility that Drd3-mediated PKA inhibition in inhibitory neurons may promote the endocytosis of GABAA receptors, thereby suppressing GABA-receptor-mediated inhibitory synaptic transmission (G. Chen et al., 2006; Swant et al., 2008). Given that LS neurons are predominantly GABAergic, future studies addressing whether a PD128907 treatment modulates GABAA receptor trafficking in the LS Drd3 neurons or whether ESD-induced blunting of LS Drd3 neuronal activity is linked to an increase in GABAA receptor density on plasma membranes. These studies could provide critical mechanistic insights into how Drd3 signaling contributes to social dysfunction following ELS.

3.2. Lateral hypothalamic LepR in ELT-induced binge eating

Binge eating is characterized by the consumption of unusually large amounts of food within a short period, often triggered by emotional distress. Binge eating disorder (BED), the most common eating disorder, involves recurrent episodes of binge eating accompanied by feelings of loss of control, even in the absence of hunger (Bulik et al., 2007; Grissett and Fitzgibbon, 1996). Importantly, clinical studies suggest adults with BED often report experiencing certain forms of early life trauma (ELT), such as the loss of a family member or economic hardship, underscoring the role of ELT in the development of binge eating behaviors later in life (Grilo and Masheb, 2001; Wonderlich et al., 1997). Therefore, elucidating the specific neural mechanisms by which ELT contributes to binge eating could facilitate the development of more effective therapies for BED and obesity.

Leptin, a hormone derived from adipose tissue, exerts its anorexic effects by acting on its receptors in the hypothalamus and regulating neural activity (Tartaglia et al., 1995; Zhang et al., 1994). Activation of the leptin receptor (LepR) triggers multiple signal transduction pathways that involve phosphorylation of signal transducer and activator of transcription3 (STAT3), which suppresses food intake and prevents weight gain (Bates et al., 2003). In the 2022 study by Shin et al. (2022), the authors demonstrated that LepR signaling is selectively reduced in the LH but not in the arcuate nucleus or ventromedial hypothalamus of animals exposed to ELT. Behaviorally, adult ELT mice showed augmented and sustained binge eating of HFD during repeated cycles of intermittent HFD access — a condition known to provoke HFD withdrawal-induced emotional overeating (Czyzyk et al., 2010). These findings suggest that reduced LepR signaling in the LH may play a key role in driving binge eating behaviors in ELT mice. Moreover, this idea was further substantiated by the experiment in which shRNA-mediated LepR knock-down in the LH of control mice induced sustained binge eating and weight gain, recapitulating the phenotypes of ELT mice.

At the circuit level, LepR-expressing LH (LH LepR) neurons send projections to multiple brain structures and form synapses primarily with the three downstream areas, such as the medial preoptic area (MPA), ventral tegmental area (VTA), and ventrolateral periaqueductal gray (vlPAG). The study demonstrated that vlPAG-projecting LH LepR neurons (LH LepR → vlPAG) and MPA-projecting LH LepR neurons (LH LepR → MPA) neurons represent mostly distinct neuronal populations based on relative fiber density across the brain. Behaviorally, chemogenetic activation of LH LepR → vlPAG, but not LH LepR → MPA, can increase binge consumption of HFD, while the inhibition of the LH LepR → vlPAG circuit normalizes the binge eating and obesity-prone features in ELT mice. Overall, this study reveals a circuit-specific contribution of LH LepR neurons in controlling binge eating, suggesting that ELT-induced selective reductions in LepR signaling alter LH-to-vlPAG circuit activity, promoting binge eating and obesity in later life.

In summary, this study delineated a new pathway in mice—through LH LepR neuronal projections to the vlPAG—that is a critical component for binge eating habits and HFD-induced obesity associated with ELT. Notably, the ELT paradigm employed in this study involved 3-day-old mouse pups, a developmental stage analogous to human infancy. Given evidence from human studies linking childhood maltreatment (before 18 years of age) to psychopathology in adulthood, further investigations into the effects of ELT beyond postnatal day 3 (P3) on maladaptive eating behaviors are warranted. Additionally, since ELT disrupts the so-called “stress hypo-responsive period” by elevating corticosterone levels (Levine, 1994), future research should explore the interplay between HPA axis activity and the leptin system during early development. Such studies could deepen our understanding of how ELT induces long-term consequences, including pathological binge eating.

4. Conclusion

The critical role of brain receptor molecules in mediating behavioral stress responses is increasingly evident in recent research. Notably, brain receptor molecules act as key gateways for external chemical signals, transducing environmental stressors into neuronal responses that determine stress-coping strategies. This review highlights how receptor molecules such as mGluR5, GR, Drd3, and LepR in specific brain regions like NAc, LH, and LS modulate resilience, emotional/binge eating, and sociability under stress. Through a multidisciplinary approach, studies uncover how these receptors drive maladaptive changes in synaptic plasticity or circuit activity, leading to behavioral dysfunctions following traumatic stress experienced in early life or adulthood. Future research should continue exploring how targeted manipulation of these receptors could potentially guide the development of novel, receptor-specific treatments that address the symptom-specific psychiatric outcomes after different types of stressful events. This may provide improved therapeutic strategies that are precise, effective, and tailored to individual stress vulnerabilities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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