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Current Perspective

Roles of Dopamine and Inflammation-Related Molecules in Behavioral Alterations Caused by Repeated Stress

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Abstract. Prolonged or intensive stress results in emotional and cognitive deficits and is a major risk factor for psychiatric disorders such as depression. Since the molecular mechanisms of how biological adaptations to stress go awry remains elusive, pharmaceutical development targeting stress has not been established. In rodents, repeated stress alters functions of multiple brain areas including the medial prefrontal cortex (mPFC) that confers stress resilience, thereby causing depression, anxiety, and working memory deficit. The mesocortical dopaminergic pathway that regulates such stress-coping functions is attenuated with repetition of stress via prostaglandin (PG) E_2, a bioactive lipid derived from arachidonic acid, and its receptor EP1. Several findings suggest that microglia activated by repeated stress are involved in emotional and cognitive changes as a source of inflammation-related molecules such as PGE_2 and IL-1β. IL-1 signaling is critical not only for emotional changes but also for microglial activation induced by repeated stress. Furthermore, purinergic signaling via the P2X7 receptor that can trigger PGE_2 and IL-1β production in microglia has been implicated in the pro-depressive effect of repeated stress as well as depressive disorders. Collectively, inflammation-related molecules that link repeated stress to mPFC dysfunction are potential targets of pharmaceutical development for psychiatric disorders.

Keywords: stress, prefrontal cortex, dopamine, prostaglandin E_2, microglia

1. Introduction

Environmental insults, regardless of the type of stimuli, cause a typical sequence of biological responses in many mammalian species. The term 'stress' has been coined to postulate a biological entity that evokes such typical biological responses. Accordingly, the stimuli that evoke stress and the responses that are evoked by stress are called stressors and stress responses, respectively. In general, animals cope with stress through altered homeostasis, such as increased glucocorticoid release and decreased reproductive and immune functions. Whereas these adaptive changes are strategic to reallocate energy for their immediate demands, they come with costs. Thus, prolonged or intensive stress results in various dysfunctions of the body including depression, anxiety, impaired attention and memory, and sleep disturbance as well as increased risks for cardiac, metabolic, and gastrointestinal diseases. Indeed, epidemiological studies have suggested stress as a major risk factor for psychiatric disorders, such as major depression and post-traumatic stress disorder. However, since the mechanisms that underlie functional changes associated with stress remain elusive, pharmaceutical development that targets stress has not been established.

Previous studies with rodents have shown that repeated stress alters the function of multiple brain areas implicated in emotion and cognition (1 – 5). Among these brain areas, the medial prefrontal cortex (mPFC) is critical for stress resilience that suppresses behavioral depression induced by repeated stress (6 – 9). The mesocortical dopaminergic pathway that regulates such stress-coping

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functions is attenuated with repetition of stress, enabling stress to cause behavioral depression and working memory impairment (9, 10). This dopaminergic attenuation is mediated by prostaglandin (PG) E_2, a bioactive lipid derived from arachidonic acid, and its receptor EP1 (9). Several lines of evidence suggest that microglia activated by repeated stress act as a cellular source of inflammation-related mediators, such as PGE_2 and IL-1β, in the brain and contribute to stress-induced behavioral changes (9, 11, 12). In this review, I will summarize these recent findings, which potentially contribute to pharmaceutical development for psychiatric disorders.

2. Structural and functional alterations of multiple brain areas with repeated stress

In rodents, repeated exposure to stress, such as repeated restraint stress and chronic mild stress, alters the structure and function of multiple brain areas, including prefrontal cortices and the hippocampus. Previous studies suggest that chronic stress reduces the number and length of dendrites of pyramidal neurons in the medial prefrontal cortex (mPFC) (1, 2) and the CA3 region of the hippocampus (3), whereas these measures of dendrites are increased in the orbitofrontal cortex (1). However, care should be taken to interpret these results, because changes in neuronal morphology depend on the duration and type of stressors.

Behavioral experiments show that repeated stress induces cognitive and emotional changes consistent with the structural changes described above. For example, repeated stress impairs attentional set shifting, spatial working memory, and extinction of fear conditioning, all of which depend on the integrity of the mPFC (1, 2, 4). Hippocampus-dependent spatial long-term memory is also impaired (3, 4). In contrast, repeated forced swim stress facilitates reversal learning that the stimulus-reward designation is switched, a task dependent on the orbitofrontal cortex (5). Given such a specific pattern of structural and functional alterations, repeated stress appears to cause functional adaptation of the brain, rather than mere brain atrophy.

3. A role for the mPFC in depressive behaviors induced by repeated stress in rodents and its implication to human depression

Many rodent studies suggest a role for the mPFC in regulating the behavioral effect of repeated stress. For example, the infralimbic subregion of the mPFC is required for stress resiliency conferred by environmental enrichment that suppresses induction of depressive and anxiety-like behaviors by repeated stress (6). The rapid antidepressant action of ketamine also requires the mTOR pathway in the mPFC (7). Furthermore, optogenetic stimulation of mPFC neurons suppresses depressive behaviors, such as social avoidance and reduced sucrose preference, induced by repeated social defeat stress (8).

Since stress is thought to be a major risk factor for depressive disorders, it is worth mentioning that the volume of the mPFC, especially the subgenual prefrontal cortex, a functional equivalent to the rodent infralimbic cortex, is decreased in depressive patients (13). Deep brain stimulation targeted to the white matter tract adjacent to the subgenual prefrontal cortex has successfully reduced depressive symptoms in about a half of treatment-resistant patients (14), highlighting the importance of the mPFC in pathophysiology of depressive disorders. Given the stress-coping function of the mPFC, its dysfunction could cause stress susceptibility, thereby leading to the depressive symptoms of these patients.

4. Attenuation of the mesocortical dopaminergic pathway with repetition of stress and its functional implications

Dopamine is a neuromodulator implicated in various neural functions ranging from motor control, motivational behavior, and attention. Distinct populations of dopamine neurons mainly located in the midbrain project to different dopaminoceptive areas, such as the dorsal striatum, the nucleus accumbens (NAc), and the mPFC. Among those several dopaminergic pathways, the mesocortical dopaminergic pathway, of which dopamine neurons in the ventral tegmental area (VTA) project to the mPFC, has been implicated in neural responses to stress. However, whether and how such dopaminergic responses to stress are related to emotional and cognitive changes associated with repeated stress has remained unclear.

To address this issue, we subjected mice to single or repeated social defeat stress and examined dopamine turnover, a biochemical index for dopamine release, in the mPFC and the NAc (9). Single exposure to social defeat increased dopamine turnover in the mPFC, but much less in the NAc, suggesting the preferential activation of the mesocortical dopaminergic pathway upon acute stress. The dopaminergic response in the mPFC was attenuated with the repetition of stress, and stress-induced c-Fos expression in VTA dopamine neurons was similarly attenuated by repeated stress. It was reported that prolonged social isolation, another form of stress associated with behavioral depression, also decreases dopamine turnover in the mPFC (15). Therefore, chronic stress appears to attenuate the activity of mesocortical dopamine neurons regardless of the type of stressors.

Several findings suggest that this attenuation of the mesocortical dopaminergic pathway underlies the induction of depressive behaviors by repeated stress (9). First, a negative correlation is observed between the dopaminergic response in the mPFC and the level of social avoidance after repeated social defeat stress. Second, a dopaminergic lesion in the mPFC by local injection of 6-hydroxydopamine, with noradrenergic and serotonergic terminals spared, facilitates induction of social avoidance, such that the lesioned mice show social avoidance even with only a single exposure to social defeat, which rarely induces social avoidance in sham-operated mice. The attenuation of the mesocortical dopaminergic pathway also accounts for the spatial working memory deficit associated with repeated stress, since this behavioral deficit can be ameliorated by local injection of a dopamine D_1-like–receptor agonist to the mPFC (10). These findings suggest that stress-induced activation of the mesocortical dopaminergic pathway confers stress resilience, but is attenuated with the repetition of stress, leading to emotional and cognitive alterations (Fig. 1).

Studies on the role of dopamine in major depression remain relatively scarce so far. In vivo microdialysis experiments have shown that antidepressants with different pharmacological actions consistently augment dopamine release in the mPFC, but not in the NAc (16). Although this finding implicates the mesocortical dopaminergic pathway in therapeutic actions of antidepressants, whether this dopaminergic pathway is impaired in the brains of depressive patients remains elusive.

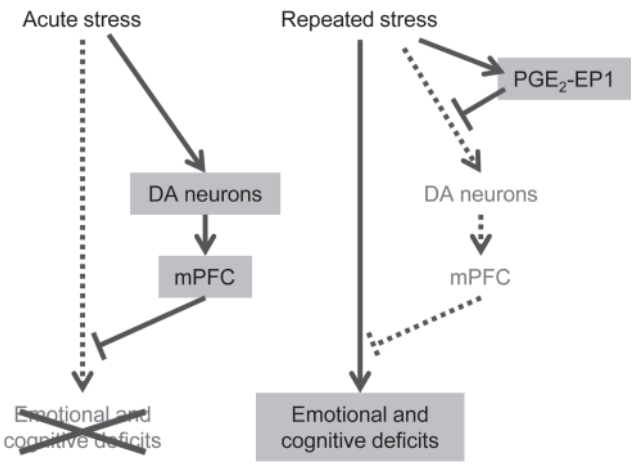

Fig. 1. Stress-coping functions of the mesocortical dopaminergic pathway and their attenuation with repetition of stress by PGE_2–EP1 signaling. Acute stress activates VTA dopamine neurons projecting to the mPFC, conferring stress resilience that interferes with the behavioral effect of stress. Repeated stress activates PGE_2–EP1 signaling, which attenuates the stress-induced activation of mesocortical dopamine neurons. The attenuation of the mesocortical dopaminergic pathway as such enables stress to cause emotional and cognitive deficits. Solid and dotted lines represent the pathways that are active and inactive, respectively.

5. Distinct functions of the mesocortical and mesoaccumbal dopaminergic pathways in stress

In contrast to the attenuation of the mesocortical dopaminergic pathway, it has been shown that repeated social defeat stress increases firings of VTA dopamine neurons for at least several weeks after the last defeat episode (17, 18). This increased excitability is accompanied by augmented Ih currents through hyperpolarization-activated cyclic nucleotide gated (HCN) channels (18). Local infusion of HCN-channel blocker at one week following the last defeat episode ameliorates depressive behaviors such as social avoidance and reduced sucrose consumption (18). These findings indicate that increased excitability of VTA dopamine neurons contributes to the expression, if not the induction, of depressive behaviors after repeated stress.

Previous studies suggest that VTA dopamine neurons exert this pro-depressive action through the NAc shell. It has been shown that selective knockdown of BDNF in VTA neurons abolishes depressive behaviors (17). VTA neurons are the primary source of BDNF proteins in the NAc. Consistent with increased excitability of VTA dopamine neurons, repeated stress increases BDNF in the NAc. Furthermore, BDNF infusion to the NAc decreases social interaction after social defeat, and blockade of intracellular signaling of BDNF, such as ERK and CREB, in the NAc shell abolishes behavioral depression induced by repeated social defeat stress. These results suggest that repeated stress increases BDNF in the NAc through the mesoaccumbal dopaminergic pathway, thereby promoting the expression of depressive behaviors (Fig. 2).

Given the function of the mesocortical dopaminergic pathway and its alteration with repeated stress, as described above, the mesocortical and mesoaccumbal dopaminergic pathways appear to behave differently with repetition of stress and to play distinct roles in suppressing and facilitating depressive behaviors, respectively (Fig. 2). Although the mechanism for these differences remains elusive, each population of dopamine neurons may receive a distinct pattern of innervations (19). Furthermore, it was reported that mesocortical dopamine neurons lack HCN currents that are present in conventional slow-firing dopamine neurons (20). Since the suppression of dopaminergic activity in the mPFC augments stress-evoked dopamine release in the NAc (21), it is also plausible that the attenuation of the mesocortical dopaminergic pathway underlies the facilitation of the mesoaccumbal dopaminergic pathway by repeated stress. Distinct functions of these dopaminergic pathways as

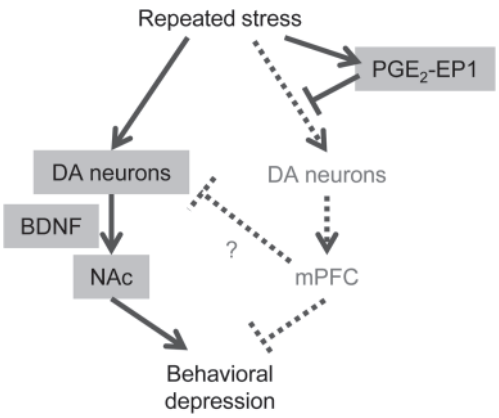

Fig. 2. Distinct functions of the mesocortical and mesoaccumbal dopaminergic pathways in repeated stress. Whereas repeated stress attenuates the mesocortical dopaminergic pathway via PGE_2–EP1 signaling, it has been suggested that the same stress increases the excitability of the mesoaccumbal dopaminergic pathway, which underlies behavioral depression via BDNF action in the NAc. Although it has been shown that dopaminergic suppression in the mPFC augments dopamine release in the NAc upon acute stress, whether such interplay between the two dopaminergic systems is involved in repeated stress remains to be examined. Solid and dotted lines represent the pathways that are active and inactive, respectively.

illustrated in repeated social defeat stress may also be applied to another form of stress, since it was reported that prolonged social isolation increases the dopamine turnover in the NAc, but decreases the dopamine turnover in the mPFC (15).

6. A role for PGE_2–EP1 signaling in the induction of behavioral depression by repeated stress

We have described so far alteration of the dopaminergic pathways by repeated stress and its implication in emotional and cognitive changes. Our recent findings have further shown the critical role for PGE_2, a bioactive lipid derived from arachidonic acid, and its receptor EP1 in both the behavioral and dopaminergic changes associated with repeated stress (9).

PGE_2 is a bioactive lipid derived from arachidonic acid by sequential actions of cyclooxygenase (COX) and PGE synthase. PGE_2 then binds for its functions to four cognate G protein-coupled receptors, named EP1, EP2, EP3, and EP4, each of which is mainly coupled to distinct intracellular signaling pathways (22). Originally, roles of PGE_2 and its receptors have extensively been studied in stress responses associated with peripheral inflammation composed of fever, hypothalamus–pituitary–adrenal (HPA) activation, hyperalgesia, hypersomnia, lethargy, depression, and so forth. Recently, several clinical reports have shown that NSAIDs, such as celecoxib, augment the therapeutic effects of conventional antidepressants (23). Although these findings suggest a potential role for PG signaling in the pathogenesis of depressive disorders, it is not conclusive, given the multiple pharmacological actions of NSAIDs.

To examine the role of PG signaling in behavioral depression, we subjected mice lacking the respective PGE receptors to repeated social defeat stress and examined stress-induced depressive behaviors (9). EP1-deficient mice, but not those lacking other PGE receptors, failed to show social avoidance and elevated anxiety induced by repeated social defeat stress. In contrast, EP1 deficiency did not affect the immediate responses to social defeat, such as submissive posture. EP1-deficient mice also showed a normal immediate rise in serum glucocorticoid levels upon social defeat, despite the critical role of EP1 in the HPA activation by peripheral inflammation (22). Thus, EP1 appears to be critical for translating repeated stress to long-term emotional changes, but not for stress perception.

In addition, EP1 deletion abolishes dopaminergic changes with repetition of stress that are observed in wild-type mice, such as the attenuation of mPFC dopamine turnover and that of c-Fos expression in VTA dopamine neurons (9). In contrast, EP1 deficiency does not affect the prefrontal dopaminergic response upon single stress exposure. Thus, EP1 is critical for the attenuation of the mesocortical dopaminergic pathway by repeated stress. Notably, receptors for other stress-related molecules, such as glucocorticoid and corticotropin-releasing hormone, are involved in the facilitation of prefrontal dopamine release upon acute stress (24, 25). Therefore, distinct molecules could regulate prefrontal dopamine release under acute and chronic stress (Fig. 3).

EP1-mediated attenuation of the mesocortical dopaminergic pathway appears to be involved in behavioral depression, since systemic administration of SCH23390, a dopamine D_1-like–receptor antagonist, restores social avoidance in EP1-deficient mice (9). In this experiment, SCH23390 was administered during stress exposure, but not at the time of the social avoidance test. This result is consistent with the role of the mesocortical dopaminergic pathway that counteracts the behavioral effect of stress and suggests that the PGE_2–EP1 signaling activated by repeated stress attenuates this dopaminergic function, thereby leading to behavioral depression (Fig. 1).

Since infusion of ONO-DI-004, an EP1 agonist, to the cerebral ventricle reduces aggressive behavior evoked by electric foot shock (22), the action of EP1 within the brain can regulate emotional behaviors. Indeed, PGE_2–EP1 signaling appears to act on and to augment inhibitory synaptic inputs to midbrain dopamine neurons (22).

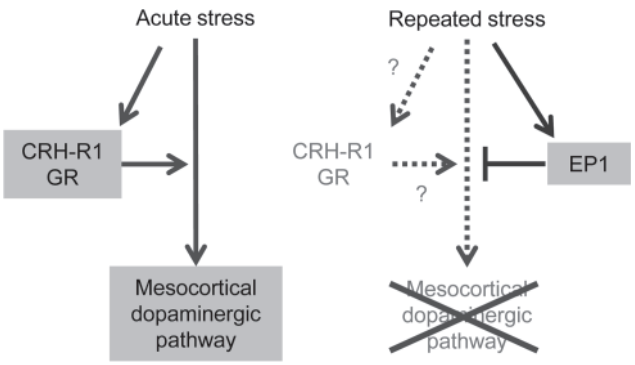

Fig. 3. Distinct stress-related molecules involved in the regulation of the mesocortical dopaminergic pathway upon acute and repeated stress. Whereas PGE_2–EP1 signaling is critical for the attenuation of the mesocortical dopaminergic pathway with repeated stress, the lack of this signaling does not affect the mPFC dopaminergic response upon acute stress. In contrast, it has been shown that corticotropin-releasing hormone receptor I (CRH-RI) and glucocorticoid receptor (GR) are involved in the facilitation of the mesocortical dopaminergic pathway upon acute stress. The role for CRH-RI and GR in repeated stress remains unknown. Solid and dotted lines represent the pathways that are active and inactive, respectively.

Thus, bath application of ONO-DI-004 augments inhibitory postsynaptic currents measured from dopamine neurons in midbrain slices, and EP1 immunoreactivity was detected at GABAergic terminals apposed to dopamine neurons. Since EP1 is primarily coupled to intracellular Ca^{2+} increase in the heterologous expression system (22), EP1-mediated Ca^{2+} increase at the GABAergic terminals could facilitate GABA release onto dopamine neurons, leading to suppression of these neurons.

However, since EP1 expression was reported in other brain areas, such as the striatum, amygdala, and hypothalamus (22), and even in peripheral immune cells, potential involvement of EP1 in any of these structures or cells in repeated stress cannot be excluded. For example, PGE_2–EP1 signaling critically augments the signaling efficacy of dopamine D_1-like and D_2-like receptors in medium spiny neurons of the striatum including the NAc (22). Since the increased excitability of mesoaccumbal dopamine neurons appears to underlie behavioral depression by repeated stress (17), EP1-mediated facilitation of dopamine-receptor signaling in the NAc may also contribute to behavioral depression.

Although the site of EP1's action in repeated stress remains to be established, our findings clearly demonstrate an unexpected link between PGE_2 signaling activated by repeated stress and dopaminergic dysfunction in mPFC that leads to stress susceptibility.

7. Microglial activation associated with repeated stress and its functional implication

Given the importance of PGE_2 in the behavioral and dopaminergic changes caused by repeated stress, a critical question is how repeated stress leads to PGE_2 synthesis. COX is an enzyme critical for PGE_2 synthesis. There are two COX isoforms, COX-1 and COX-2, with different distributions and functions (22). Genetic deletion of COX-1, but not that of COX-2, interferes with induction of social avoidance by repeated social defeat stress (9). Systemic administration of SC-560, a COX-1 selective inhibitor, but not that of SC-236, a COX-2 selective inhibitor, also abolishes social avoidance induced by repeated stress. Thus, selective involvement of COX-1 in repeated social defeat stress has been demonstrated.

Several groups including ours have reported that repeated stress increases the PGE_2 content in the brain (9). Given that COX-1 expression in the brain is enriched in microglia (9, 26), PGE_2 synthesized by microglial COX-1 could be involved in repeated social defeat stress (Fig. 4). Consistent with this notion, several groups including ours have suggested microglial activation with repeated stress. After repeated social defeat stress, microglia show histological markers for microglial activation, such as hyper-ramified morphology and increased Iba-1 immunoreactivity, in various brain areas such as the VTA, NAc, and the mPFC (9, 11, 12). In addition, stress exposure alters gene expression profiles of microglia and primes microglia for cytokine production upon subsequent stimulation (12, 27). Such microglial activation appears to be involved in behavioral changes induced by repeated stress. For example, genetic deletion of IL-1 receptor type I abolishes histological changes associated with microglial activation as well as elevated anxiety induced by repeated social defeat stress (12). In addition, systemic treatment with minocycline, a drug that inhibits microglial activation by a yet-unknown mechanism, during stress exposure prevents repeated restraint stress from inducing working memory deficit (11).

Whereas microglia act as a major source of inflammation-related mediators, recent evidence suggests that microglia "survey" microenvironments with their processes engulfing cellular debris, such as the neighboring synaptic apparatus being removed. It was reported that the genetic deletion of complement receptor 3 impairs the phagocytosis of the synaptic apparatus by microglia as well as morphological plasticity of axons of retinoganglionic cells during postnatal development (28), suggesting the role of microglia in morphological plasticity of neurons. Since repeated stress alters dendritic morphology of neurons in various brain areas (1 – 3), the potential involvement of activated microglia in such structural al-

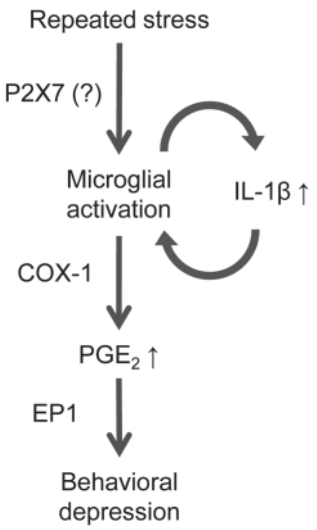

Fig. 4. Stress-induced activation of microglia as a potential source of inflammation-related molecules. Several studies have suggested that repeated stress activates microglia, and such microglial activation appears to be involved in stress-induced emotional and cognitive changes. Given the role of COX-1, a PG synthase expressed in microglia, in behavioral depression, activated microglia could contribute to PGE_2 synthesis and subsequent activation of EP1 upon repeated stress. IL-1 signaling is critical for stress activation of microglia. Since microglia are the major source of IL-1β, IL-1 signaling may constitute a positive feedback loop for microglial activation. The purinergic P2X7 receptor has been implicated in behavioral depression induced by repeated stress as well as genetic susceptibility to depressive disorders. P2X7-receptor activation is known to induce IL-1β and PGE_2 production in microglia. Therefore, the P2X7 receptor could be activated upon repeated stress for microglial activation, although this possibility remains to be tested.

terations is an intriguing question for future research.

8. Potential mechanisms for microglial activation in repeated stress

As described above, IL-1 signaling appears to be critical for microglial activation, since genetic deletion of IL-1 receptor type I abolishes microglial activation induced by repeated social defeat stress (12). Cell-type specific expression analysis has detected IL-1β expression in CD11b-positive cells including microglia, but not CD11b-negative cells, in the hippocampus (29). Since repeated stress increases IL-1β mRNA expression in isolated CD11b-positive cells (12), IL-1 signaling may constitute a positive feedback loop for microglial activation in repeated stress (Fig. 4).

Since stress is thought to be the way the brain perceives stressors, it is plausible that some neuron-derived substance is involved in microglial activation by repeated stress. Indeed, propranolol, a β-adrenergic receptor antagonist, suppresses stress-induced microglial activation (12), suggesting the role of noradrenaline in microglial activation. There are many candidate molecules that mediate neuron–microglia crosstalk. For example, membrane-bound molecules present on the cell surface of neurons, such as fractalkine and CD200, are implicated in holding microglia in the quiescent state, and it was reported that stress exposure reduces expression of CD200 (27). In addition, at least in pathological conditions associated with pain and epilepsy, neurons secrete damage-associated molecular pattern molecules, such as ATP and high mobility group box 1, that can activate microglia. Notably, genetic deletion of purinergic P2X7 receptor abolishes the pro-depressive effect of repeated stress, as measured by immobility during the forced swim test (30). In addition, genetic variants of the P2X7 receptor have been associated with increased risk of mood disorders (31). Since ATP can evoke production of IL-1β (32) and COX-1-dependent PGE_2 release from microglia (26) through the P2X7 receptor, this purinergic receptor could be activated upon repeated stress and trigger microglial activation to induce further production of inflammation-related mediators upon repeated stress (Fig. 4).

9. Conclusions

In this review, I described the stress-coping function of the mesocortical dopaminergic pathway and its attenuation with repetition of stress. Since the mesocortical and mesoaccumbal dopaminergic pathways play distinct roles in repeated stress, investigating the mechanism selectively involved in each of these dopaminergic pathways, rather than dopaminergic regulation in general, may offer better molecular targets of pharmaceutical development for psychiatric disorders.

One such molecular candidate is the PGE_2–EP1 signaling pathway, given its critical role in the attenuation of the mesocortical dopaminergic pathway induced by repeated stress. Since repeated stress appears to activate microglia as a primary source of inflammation-related mediators, such as PGE_2 and IL-1β, to identify inflammation-related molecules and their actions involved in repeated stress paves the way for revealing neuron–microglia crosstalk in repeated stress. Given the proposal of a positive feedback loop for microglial activation via IL-1β, drugs that suppress microglial activation upon stress may help interfere with a malicious cycle of molecular events that maintain the pathological state of the stressed brain.

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