

Nuclear factor- κ B is a critical mediator of stress-impaired neurogenesis and depressive behavior

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Proinflammatory cytokines, such as IL-1 β , have been implicated in the cellular and behavioral effects of stress and in mood disorders, although the downstream signaling pathways underlying these effects have not been determined. In the present study, we demonstrate a critical role for NF- κ B signaling in the actions of IL-1 β and stress. Stress inhibition of neurogenesis in the adult hippocampus, which has been implicated in the prodepressive effects of stress, is blocked by administration of an inhibitor of NF- κ B. Further analysis reveals that stress activates NF- κ B signaling and decreases proliferation of neural stem-like cells but not early neural progenitor cells in the adult hippocampus. We also find that depressive-like behaviors caused by exposure to chronic stress are mediated by NF- κ B signaling. Together, these data identify NF- κ B signaling as a critical mediator of the antineurogenic and behavioral actions of stress and suggest previously undescribed therapeutic targets for depression.

cytokine | IL-1 | inflammation | neural progenitor cell | depression

Mood disorders represent a major health concern, affecting over 15% of the population in developed countries, resulting in enormous personal and economic costs and, in many cases, suicide (1, 2). Despite significant efforts, the neurobiological mechanisms underlying depression have not been characterized. Both genetic and environmental factors contribute to depression, and traumatic or repeated stress is known to precipitate or exacerbate mood disorders (3–5). In addition, proinflammatory cytokines, including IL-1 β , IL-6, and TNF- α , that are induced by injury and infection as well as by psychological stress have been implicated in depressive behavior in rodent models and depressed patients (6–8).

Exposure to stress and depression can result in atrophy of limbic brain regions that control emotion and mood, including inhibition of neurogenesis in the adult hippocampus (5, 9, 10). Inhibition of neurogenesis is observed with many different types of physical and psychological stressors, but the types of cells, neural stem-like cells (NSCs) or intermediate transient amplifying neural progenitor cells (ANPs), that are influenced have not been characterized (9, 11). A role for proinflammatory cytokines is supported by a recent report that IL-1 β signaling is necessary and sufficient for the antineurogenic and behavioral effects of stress (6). One possible signaling cascade that could mediate the effects of IL-1 β is NF- κ B, which is activated by IL-1 β and other cytokines both in peripheral immune cells and in the brain (8, 12). Chronic stress enhances the activation of NF- κ B in response to inflammatory stimuli (13, 14), and social stress increases NF- κ B signaling in healthy subjects and produces an exaggerated response in depressed patients (15, 16).

In the present study, we investigate the role of NF- κ B in the cellular and behavioral responses to acute and chronic stress. The results demonstrate that the inhibition of neurogenesis by stress occurs via activation of NF- κ B in NSCs and that stress-induced anhedonia, a core symptom of depression, is dependent on NF- κ B.

Results

NF- κ B Signaling Mediates the Suppression of Hippocampal Neurogenesis Caused by Acute and Chronic Stress. To examine the role of NF- κ B in the effects of acute stress, rats were adminis-

tered an inhibitor of NF- κ B before acute immobilization stress (45 min) (Fig. 1A). Two selective structurally different NF- κ B inhibitors were tested: JSH-23 (JSH) and SC-514 (SC) (17, 18). Immediately after immobilization, rats were administered BrdU, a thymidine analogue that is incorporated into dividing cells (2 h post-BrdU injection). Post hoc analysis revealed that immobilization stress significantly decreases the number of BrdU⁺ cells in the subgranular zone (SGZ) of the dentate gyrus (DG), and this effect is completely blocked by preadministration of either JSH or SC (Fig. 1B–D).

We also examined the role of NF- κ B in the antiproliferative effects of chronic unpredictable stress (CUS), a model of depression with face, predictive, and construct validity (19, 20). Exposure to CUS significantly decreased the number of BrdU⁺ cells, and this effect was completely blocked by infusion of JSH (i.c.v., minipump) (Fig. 1F). At the time point examined (14 days after BrdU) (Fig. 1E), the majority of the BrdU⁺ cells express doublecortin (DCX), a marker of immature neurons (Fig. 1H). Analysis of the BrdU⁺ DCX⁺ double-labeled cells demonstrates that CUS also decreases the number of immature neurons, and this effect was blocked by JSH (Fig. 1G).

Acute Stress Decreases the Proliferation of NSCs: Blockade by NF- κ B Inhibition. We next examined the influence of acute immobilization stress (45 min) on the two major classes of progenitors. NSCs undergo asymmetric division, are self-renewing, have a radial glial morphology, and express GFAP and the transcription factor sex-determining region Y-box containing gene 2 (SOX2) (21–23) (Fig. 2A). ANPs undergo symmetric division and express SOX2 but not GFAP (22, 23). In the current study, we found that nearly all BrdU⁺ cells were SOX2⁺ (97.1 \pm 1.5%), and exposure to acute immobilization stress significantly decreased the number of BrdU⁺ SOX2⁺ double-labeled cells. Importantly, this effect of stress was completely blocked by pretreatment with the NF- κ B inhibitor JSH (Fig. 2B). We also found that acute stress significantly decreases the number of triple-labeled NSCs (BrdU⁺ SOX2⁺ GFAP⁺) (Fig. 2C) but not the number of ANPs (BrdU⁺ SOX2⁺ GFAP[−]) (Fig. 2D), and this effect is blocked by JSH pretreatment.

Previously, we have shown that the antineurogenic effects of stress occur via IL-1 β /IL-1 receptor type I (RI) signaling, both in vivo and in vitro (6). We found that IL-1RI is expressed in both NSCs and ANPs, albeit at different levels (27.6 \pm 2.2% and 49.2 \pm 6.3%, respectively) (Fig. S1). Because the majority of the SOX2⁺ cells are GFAP⁺ NSCs (81.3 \pm 1.4%), there are more NSCs than ANPs that express IL-1RI.

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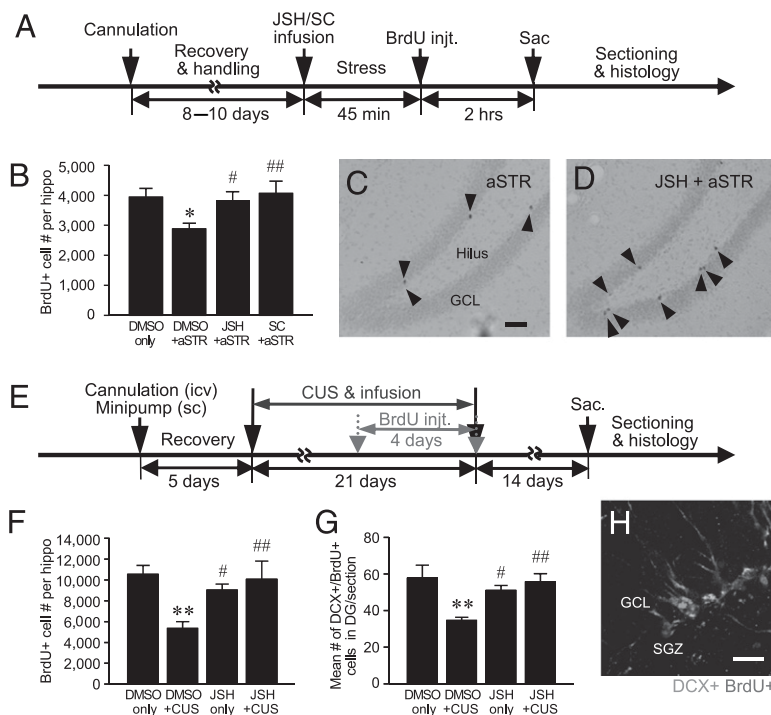


Fig. 1. Effects of stress and NF- κ B inhibitors on hippocampal neurogenesis in rats. (A) Schematic depicting the experimental procedures for acute stress (aSTR). After 8–10 days of recovery and handling, rats were infused (i.c.v.) with the NF- κ B inhibitors JSH or SC or with vehicle (DMSO) before immobilization and were then killed (sac) 2 h after BrdU administration. injt., injection. (B) aSTR decreased the number of BrdU $^{+}$ cells in the DG of the hippocampus. The effect of aSTR was blocked by either JSH or SC (one-way ANOVA: $F_{3,26} = 3.527$, $P < 0.05$; $n = 7$ –8 per group). Dividing BrdU $^{+}$ cells (black arrowheads) in the DG of acute-stressed (C) and JSH-infused stressed (D) rats. GCL, granular cell layer. (Scale bar: 100 μ m.) (E) Schematic for CUS. Rats were implanted with a cannula (i.c.v.) and minipump (s.c.), were exposed to two stressors per day for 21 days, received BrdU daily for the last 4 CUS days, and were killed 14 days later. JSH blocked the effects of CUS on BrdU $^{+}$ cells ($F_{3,19} = 5.013$, $P < 0.05$; $n = 5$ –6 per group) (F), and immature neurons were measured as the number of BrdU $^{+}$ (red) DCX $^{+}$ (green) double-labeled cells per hippocampal DG ($F_{3,12} = 6.250$, $P < 0.01$; $n = 4$ per group) (G and H). (Scale bar: 25 μ m.) By one-way ANOVA followed by the Fisher's PLSD test, * $P < 0.05$ and ** $P < 0.01$ compared with control (DMSO) and #, $P < 0.05$ and ##, $P < 0.01$ compared with stressed animals.

Acute Stress Activates NF- κ B Signaling in NSCs. We examined the cellular localization of NF- κ B activation using transgenic NF- κ B/LacZ reporter mice. Immunohistochemical analysis demonstrates that β -gal is expressed in the granule cell layer of the DG (Fig. 3 A and B), as previously reported (24). Triple-labeling studies demonstrate that β -gal is expressed in both NSCs (GFAP $^{+}$ SOX2 $^{+}$) (Fig. 3 E–I) and ANPs (GFAP $^{-}$ SOX2 $^{+}$) (Fig. 3J) in the SGZ as well as in cells in the SGZ/DG that express markers of immature (DCX) (Fig. 3K) or mature (NeuN) (Fig. 3L) neurons. Notably, proliferating newborn cells labeled with

BrdU (2 h after injection) did not express β -gal (Fig. 3 A–D), suggesting that NF- κ B activation blocks proliferation.

We also found that acute stress significantly increased the number of NF- κ B/ β -gal $^{+}$ NSCs but not ANPs in the SGZ, and this effect was blocked by pretreatment with the IL-1 receptor antagonist (Ra) (Fig. 3 M and N). This suggests that acute stress preferentially activates NF- κ B in NSCs. Stress did not change the ratio of NSCs to total progenitors in the SGZ [$F_{2,9} = 0.537$, $P =$ not significant (n.s.)]. Together, these data demonstrate that acute stress stimulates NF- κ B signaling in NSCs and that this effect is mediated by IL-1 β .

NF- κ B Signaling Underlies Depressive-Like Behavioral Effects of CUS.

To determine if NF- κ B signaling underlies the effect of CUS on depressive-like behaviors, SC was administered during 4 weeks of exposure to CUS (Fig. 4A). The novelty-induced hypophagia (NIH) test is a model of anxiety that is responsive to chronic antidepressant administration (25). CUS exposure significantly increased the latency to drink relative to nonstressed control mice in the novel cage, as determined on day 21 (Fig. 4B), and this effect is blocked by continuous infusion of SC (i.c.v., minipump). There was no difference in latency to drink in the home cage, a control for this paradigm ($F_{2,38} = 0.315$, $P =$ n.s.; $n = 13$ –15 per group) and no difference between nonstressed SC-infused (66.2 ± 14.4 s) and control (75.0 ± 19.6 s) groups in the novel cage ($t_9 = 0.345$, $P =$ n.s.; $n = 5$ –6 per group). We next tested the animals on sucrose consumption, a measure of anhedonia, which is a core symptom of depression (19, 20). CUS significantly decreased sucrose consumption, and this effect was also blocked by SC infusion (Fig. 4C). There was no difference in the consumption of tap water, a control for this test ($F_{2,21} = 0.578$, $P =$ n.s.; $n = 5$ –13 per group) and no difference in the sucrose consumption between nonstressed SC-infused (75.9 ± 2.8 mg/kg) and control (73.3 ± 3.8 mg/kg) groups ($t_{12} = 0.517$, $P =$ n.s.; $n = 6$ –8 per group).

Inhibition of NF- κ B Blocks the Antiproliferative Effects of IL-1 β in Neural Progenitor Cells in Vitro. To investigate further the mechanisms by which stress inhibits neurogenesis, studies were con-

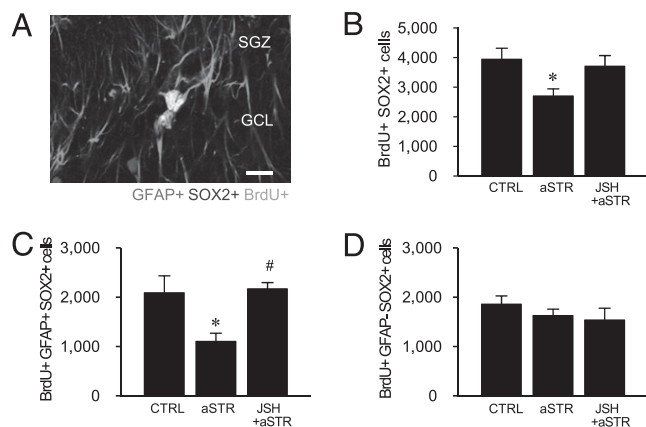


Fig. 2. Role of NF- κ B signaling in the regulation of NSC and ANP cell proliferation in acute stress. (A) Representative photograph of proliferating NSCs [GFAP $^{+}$ (red) SOX2 $^{+}$ (blue) BrdU $^{+}$ (green) cells] in the SGZ. (B) Acute stress decreased the proliferation of total progenitors (SOX2 $^{+}$ BrdU $^{+}$ cells), and there was no significant effect in CUS animals receiving JSH ($F_{2,11} = 4.215$, $P < 0.05$; $n = 4$ –5 per group). aSTR, acute stress; CTRL, control. Stress-induced impairment of NSC ($F_{2,11} = 5.814$, $P < 0.05$) (C) but not ANP ($F_{2,11} = 0.852$, $P =$ n.s.) (D) proliferation was blocked by JSH. (Scale bar: 25 μ m.) By the Fisher's PLSD test, * $P < 0.05$ compared with CTRL group and #, $P < 0.05$ compared with aSTR group.

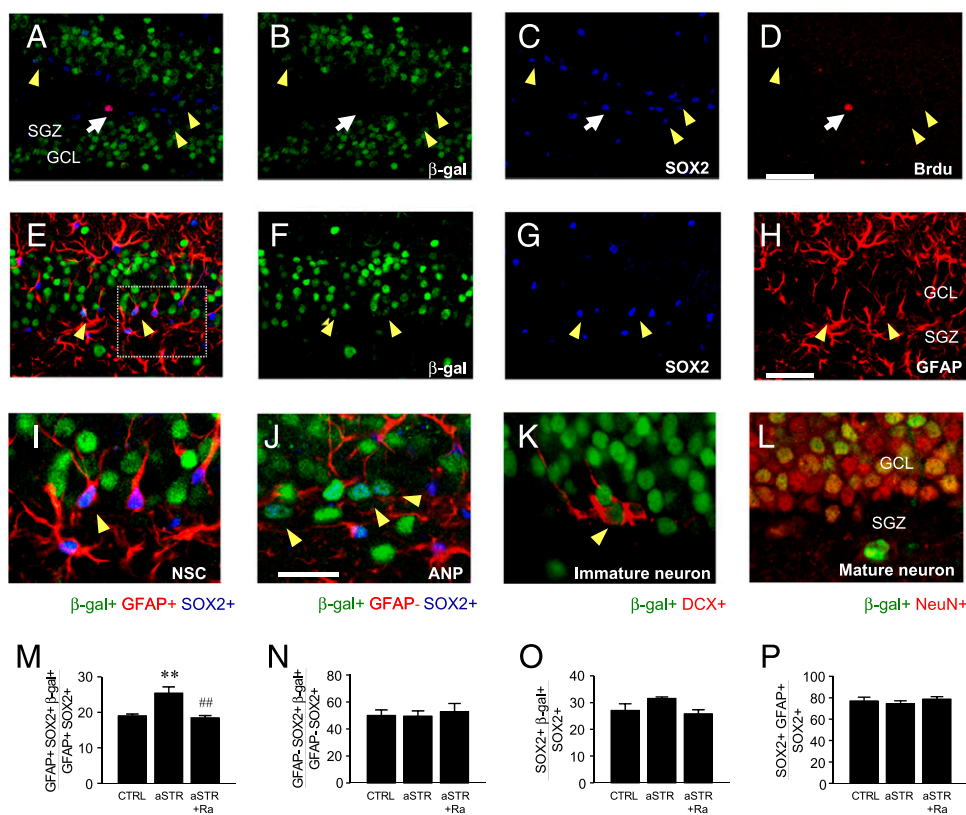


Fig. 3. Acute stress effects on NF-κB reporter expression in the hippocampus in NF-κB/LacZ reporter mice. (A–D) Most hippocampal progenitors [$\sim 94\%$; BrdU $^{+}$ (red), SOX2 $^{+}$ (blue), white arrows] did not express the NF-κB reporter [β -gal $^{+}$ (green), yellow arrowheads]. (Scale bar: 50 μ m.) (E–H) Expression of NF-κB reporter in NSCs [β -gal $^{+}$ (F, green) SOX2 $^{+}$ (G, blue) GFAP $^{+}$ (H, red)]. (Scale bar: 50 μ m.) (I) Enlarged view of NSCs from E (inset). (J) NF-κB/ β -gal was observed in ANPs (β -gal $^{+}$ SOX2 $^{+}$ GFAP $^{+}$) as well as NSCs in the SGZ. Immature [β -gal $^{+}$ DCX $^{+}$ (red)] (K) and mature [β -gal $^{+}$ NeuN $^{+}$ (red)] (L) neurons also expressed the NF-κB reporter. (M–P) Acute immobilization stress (aSTR) resulted in more NF-κB activation (β -gal $^{+}$) in NSCs but not in ANPs or in total progenitors compared with control (CTRL) [NSCs, $F_{2,9} = 11.381$, $P < 0.01$ (M); ANPs, $F_{2,9} = 0.134$, $P = \text{n.s.}$ (N); total progenitors, $F_{2,9} = 2.994$, $P = \text{n.s.}$ (O); $n = 4$ per group]. (Scale bar: 25 μ m.) By the Fisher's PLSD test, **, $P < 0.01$ compared with CTRL and #, $P < 0.01$ compared with aSTR group.

ducted on cultured adult hippocampal progenitors (AHPs). Under the culture conditions used (20 ng/mL FGF-2), $\sim 90\%$ of DAPI $^{+}$ cells expressed nestin, a marker of AHPs (Fig. S2B). Most of the nestin $^{+}$ cells ($\sim 90\%$) also incorporate BrdU, indicating that the majority of the AHPs are actively proliferating (6). Incubation with IL-1 β (2 h) significantly decreases AHP proliferation compared with vehicle, and this effect is blocked by coinubation with JSH or IL-1Ra (Fig. 5 A–C). The effect of IL-1 β was not influenced by inhibitors of corticosterone (CORT; RU486) or p38 MAPK (SB203580) (Fig. 5C). IL-1 β and CORT

decreased the ratio of BrdU $^{+}$ to nestin $^{+}$ cells but did not influence the total number of DAPI $^{+}$ cells or the ratio of nestin $^{+}$ to DAPI $^{+}$ cells (Fig. S2 A–C). In contrast, the antiproliferative effect of CORT was not influenced by JSH but was blocked by RU486 as expected and by a p38 MAPK inhibitor (SP600125; Fig. S3A). These data suggest that CORT-mediated suppression of AHP proliferation is mediated by p38 MAPK signaling and that different mechanisms underlie the antiproliferative effects of CORT and IL-1 β . Incubation with IL-1 β or CORT did not alter the ratio of TUNEL $^{+}$ to DAPI $^{+}$ cells (Fig. S3 B and C), indicating that the decrease in cell number is not a result of cell death.

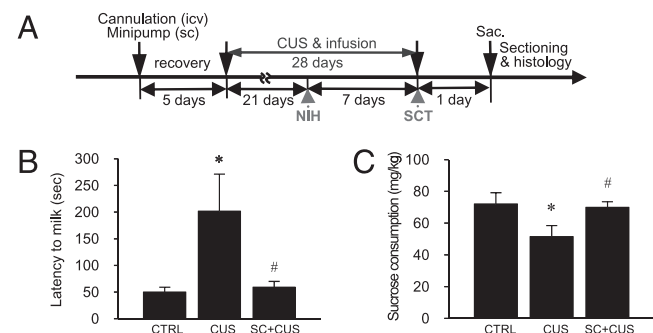


Fig. 4. Effects of CUS on depressive-like behaviors in NIH and sucrose consumption test (SCT) in mice. (A) Experimental procedures for CUS in mice. Mice were exposed to two or three stressors per day for 28 days and received BrdU daily for the last 4 days of CUS. On days 21 and 28, NIH and the SCT, respectively, were conducted. Mice were killed (sac) 24 h after the last BrdU administration. (B) CUS significantly increased latency to drink, and this effect was blocked by continuous administration of SC ($F_{2,38} = 3.748$, $P < 0.05$; $n = 13$ –15 per group). CTRL, control. (C) SC administration also blocked the effect of CUS on sucrose consumption ($F_{2,21} = 3.497$, $P < 0.05$; $n = 5$ –13 per group). By the Fisher's PLSD test, *, $P < 0.05$ compared with CTRL and #, $P < 0.05$ compared with CUS.

Discussion

The results of the current study demonstrate that inhibition of neurogenesis by acute or chronic stress is blocked by inhibition of NF-κB signaling. A requirement for NF-κB is shown using two different selective inhibitors, one that blocks IκB kinase (IKK) (SC) and the dissociation of IκB and NF-κB and one that directly inhibits NF-κB (JSH) (17, 18). Moreover, the results show that the antineurogenic effects of acute stress result from inhibition of NSC proliferation (Fig. 6). Triple-labeling studies show that the number of GFAP $^{+}$ SOX2 $^{+}$ BrdU $^{+}$ NSCs but not ANPs was significantly decreased by acute stress. These effects were confirmed in cultured hippocampal progenitor cells. Because NSCs undergo asymmetric division, giving rise to another NSC and an intermediate progenitor (i.e., ANP), the long-term consequences of inhibiting NSC proliferation (i.e., in response to CUS) would be a reduction in the pool of NSCs as well as intermediate progenitors. The ANPs then give rise to additional neurons, and decreased numbers of these cells could account for the reduction in immature neurons observed after exposure to long-term stress in the CUS paradigm.

The results also demonstrate that acute stress activates NF-κB signaling in GFAP $^{+}$ NSCs in adult hippocampus (Fig. 6), consistent with the hypothesis that NF-κB signaling in NSCs but not

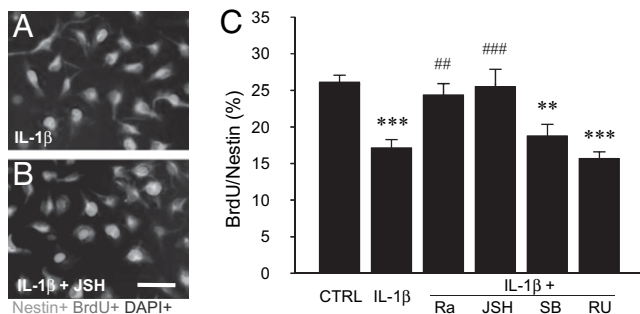


Fig. 5. Analysis of IL-1 β signaling in cultured AHPs. (A and B) Representative images of proliferating AHPs [BrdU $^{+}$ (red) nestin $^{+}$ (green)] in the presence of IL-1 β (10 ng/mL) \pm JSH (25 μ M). (C) Coincubation with IL-1Ra (Ra, 100 ng/mL) or JSH blocked the effect of IL-1 β on the ratio of BrdU $^{+}$ to nestin $^{+}$ compared with control (CTRL) ($F_{5,16} = 11.174$, $P < 0.001$; $n = 3$ –4 per group). By the Fisher's PLSD test, **, $P < 0.01$ and ***, $P < 0.001$ compared with CTRL and ##, $P < 0.01$ and ###, $P < 0.001$ compared with IL-1 β . (Scale bar: 50 μ m.)

in ANPs underlies the reduction in cell proliferation. However, the relatively small percentage of NSCs that exhibit NF- κ B/ β -gal staining (20–25%) raises a question as to whether inhibition of this population could account for a 50% reduction in NSC proliferation? There are several potential explanations for this discrepancy. One is that NF- κ B-induced gene expression is not an accurate reflection of the total level of NF- κ B activity in NSCs. This could result from low sensitivity of β -gal gene expression (i.e., NF- κ B is activated but without an increase in β -gal expression) and/or other gene transcription-independent signaling mechanisms that could influence NSC proliferation. Stress could also activate NF- κ B in surrounding cells (e.g., ANPs, neurons, glia) that indirectly influence NSC proliferation. For example, stress-induced NF- κ B activation results in generation of nitric oxide (NO) (26–28), and NO has been shown to inhibit neurogenesis in the adult hippocampus and to contribute to the inhibition of neurogenesis by stress (29, 30).

Our current results also demonstrate that activation of NF- κ B in response to acute stress is blocked by an inhibitor of IL-1RI. This is consistent with previous reports that IL-1 β /IL-1RI signaling is rapidly activated (31) and is necessary and sufficient for suppression of neurogenesis by acute stress (6). Localization studies demonstrate that IL-1RI is expressed in both NSCs and ANPs in adult hippocampus. In addition, although the percentage of NSCs that express IL-1RI is lower than that of ANPs (~25% and 50%, respectively), the ratio of IL-1RI $^{+}$ NSCs to IL-1RI $^{+}$ ANPs is ~3:1, because the total number of NSCs is much greater than the total number of ANPs. However, given the expression of IL-1RI in intermediate progenitors, it is surprising that stress selectively activates NF- κ B and inhibits proliferation of NSCs. This could result from differential localization/availability of IL-1 β in proximity to NSCs vs. ANPs or from expression of different signaling in these two populations of progenitors.

Previous studies report that NF- κ B differentially affects proliferation, maturation, and survival depending on cell type, localization, and conditions. Much of this work has focused on immune and cancer/tumor cells, in which NF- κ B is associated with cell proliferation and antiapoptotic pathways but also with proapoptotic pathways (32, 33). There is also evidence that NF- κ B activation has either prosurvival or cell death effects in the brain depending on the conditions (34–36). These effects could be explained by differential expression and activation of the multiple subtypes and components of the NF- κ B family. For example, the proapoptotic actions of NF- κ B that occur postischemia involve p50/p65, whereas c-Rel-containing dimers increase resistance to ischemia by activating antiapoptotic pathways (36). There is one report that RelA is expressed in

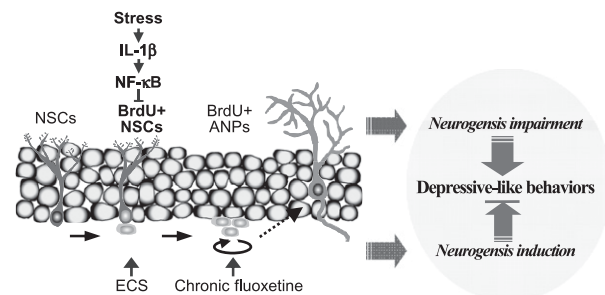


Fig. 6. Model of stress-induced impairment of NSC proliferation in the hippocampus. Stress activates IL-1 β /NF- κ B signaling, resulting in impairment of hippocampal neurogenesis and thereby contributing to depressive-like behaviors. Notably, the results demonstrate that acute stress decreases NSC proliferation and that this effect is mediated by IL-1 β /NF- κ B signaling. In contrast, antidepressant treatment increases neurogenesis by inducing NSC [electroconvulsive seizure (ECS)] or ANP (chronic fluoxetine) proliferation.

NSCs in the SVZ, whereas p50 is expressed in migrating neural precursors (37). In p50 deletion mice, there is no effect on cell proliferation in adult hippocampus under nonstress conditions (38), consistent with the negative results of the current study. Additional studies of stress in p50 mutant mice, or in conditional deletion mutants, would further characterize the role of NF- κ B family members.

Activation of the hypothalamic-pituitary-adrenal axis and elevation of glucocorticoids are typically associated with antiinflammatory responses, including inhibition of NF- κ B signaling, via inhibition of IKK and inhibition of NF- κ B transcription (17, 18). However, there are also reports that stress can increase the effects of NF- κ B, including enhancement of inflammatory responses (13, 14, 27). The current study provides another example wherein stress results in selective activation of NF- κ B signaling in a discrete population of cells, the NSCs.

We also examined the role of NF- κ B in anxiety- and depression-related behaviors after exposure to CUS. Inhibition of NF- κ B blocked the increase in latency to feed in response to CUS in the novelty suppressed feeding test (NSF) paradigm, consistent with a previous report that anxiety-related behaviors are decreased in NF- κ B/p50 null mice (39). We also found that inhibition of NF- κ B blocks the reduction in sucrose consumption resulting from CUS, an antidepressant-like effect. These findings are consistent with human studies, which demonstrate that social stress/anxiety increases NF- κ B signaling and that this effect is enhanced in depressed patients (16). Although we have focused on models that are responsive to chronic antidepressants, which are more relevant to the therapeutic response times, it would be interesting to examine other models predictive of antidepressant response (e.g., forced swim test, learned helplessness paradigm). It would also be interesting to determine if blockade of NF- κ B after exposure to stress rather than before stress, as was done in the current study, would be sufficient to reverse NF- κ B signaling and produce antidepressant behavioral effects.

In summary, the results demonstrate that IL-1 β /NF- κ B signaling is activated by stress and indicate that this signaling pathway is required for the antineurogenic and anhedonic effects of repeated stress (Fig. 6). Blockade of NF- κ B could inhibit the actions of other proinflammatory cytokines implicated in stress and depression, including IL-6 and TNF- α . Also, blockade of NF- κ B in both peripheral immune cells and the brain could provide beneficial antiinflammatory and antistress actions. The diverse and cell type-dependent actions of NF- κ B make it a complex drug target, although there may be specific cases of elevated inflammatory processes in which NF- κ B inhibitors would be useful and efficacious for the treatment of depression.

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