Lateral habenula IL-10 controls GABAergic receptor trafficking and modulates maternal separation–triggered adolescent depression

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Abstract

Maternal separation (MS) in early life is linked to adult psychiatric disorders, connecting cytokines to mood-regulating brain circuits. The Lateral Habenula (LHb), key in depression and encoding negative experiences, is influenced by MS, particularly in cytokine signaling and synaptic plasticity. Our study found two phenotypes in adolescent mice exposed to MS: depression-susceptible (SUS) and resilient (RES). SUS mice showed abnormal LHb neuron activation and inflammation, with altered pro- and anti-inflammatory cytokine levels. RNA sequencing indicated different Il10b gene expression, which codes for the IL-10 receptor, in LHb neurons between RES and SUS mice. IL-10 levels inversely related to depressive behaviors in SUS mice. IL-10 overexpression in LHb improved synaptic markers (PI3K, pAKT, gephyrin, GABAAR) and reduced GSK3β and Foxa2 expression, counteracting depression-like behaviors. Conversely, IL-10 knockdown in naive mice led to depressive behaviors, impaired GABAAR function, and disrupted PI3K/pAKT/gephyrin pathways. This highlights IL-10’s role in LHb GABAergic synaptic adaptation and the impact of early life adversity on adolescent neurobiology and mental health. These findings can guide therapeutic strategies for adolescent depression due to early life stress.

Result 1. Maternal separation induces susceptibility and depressive phenotypes in offspring mice

Figure 1. Maternal Separation (MS) induces susceptibility and depressive-like behaviors in neonatal mice. A) C57BL/6J dams were separated from pups for 2 hours on postnatal day 13 (P13) and then tested for depressive-like behaviors for 8 days. B) Injection of IL-10 into the lateral habenula (LHb) of adult mice restores the deficits in depressive-like behaviors. Right panel is the knockdown of PI3K-GSK3β signaling, which reduces PI3K/AKT and GSK3β levels in the LHb. Left panel shows the restoration of PI3K/AKT and GSK3β levels in the LHb. C) Reduced IL-10 expression in the LHb of MS-exposed mice compared to controls. D) IL-10 expression in the LHb of MS-exposed mice is positively correlated with PI3K/AKT and GSK3β levels in the LHb. E) IL-10 overexpression in the LHb of MS-exposed mice restores PI3K/AKT and GSK3β levels in the LHb. F) IL-10 overexpression in the LHb of MS-exposed mice restores PI3K/AKT and GSK3β levels in the LHb.

Result 2. Aberrant LHb hyperactivity drives the susceptibility to MS-induced depressive-like behaviors

Figure 2. Aberrant LHb hyperactivity drives the susceptibility to MS-induced depressive-like behaviors. Adolescent TAP55-AKI mice received MS during postnatal day 2 (P2) to 20 (P20) (TAP55-AKI+MS) or P2 to P9 (TAP55-AKI+SMT). A) Injection of IL-10 into the lateral habenula (LHb) of adult mice restores the deficits in depressive-like behaviors. Right panel is the knockdown of PI3K-GSK3β signaling, which reduces PI3K/AKT and GSK3β levels in the LHb. Left panel shows the restoration of PI3K/AKT and GSK3β levels in the LHb. C) Reduced IL-10 expression in the LHb of MS-exposed mice compared to controls. D) IL-10 expression in the LHb of MS-exposed mice is positively correlated with PI3K/AKT and GSK3β levels in the LHb. E) IL-10 overexpression in the LHb of MS-exposed mice restores PI3K/AKT and GSK3β levels in the LHb. F) IL-10 overexpression in the LHb of MS-exposed mice restores PI3K/AKT and GSK3β levels in the LHb.

Result 3. MS triggers inflammation and neuron-related transcriptional changes in LHb

Figure 3. MS triggers inflammation and neuron-related transcriptional changes in LHb. A) Representative immunohistochemistry (IHC) of cytokines in the LHb of MS-exposed mice. B) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. C) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. D) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. E) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. F) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. G) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. H) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. I) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. J) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. K) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. L) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. M) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. N) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. O) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. P) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. Q) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. R) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. S) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. T) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. U) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. V) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. W) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. X) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. Y) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. Z) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AA) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AB) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AC) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AD) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AE) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AF) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AG) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AH) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AI) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AJ) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AK) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AL) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AM) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AN) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AO) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AP) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AQ) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AR) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AS) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AT) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AU) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AV) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AW) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AX) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AY) Representative western blot analysis of cytokines in the LHb of MS-exposed mice. AZ) Representative western blot analysis of cytokines in the LHb of MS-exposed mice.

Graphic abstract

Maternal separation, a severe early life adversity, attenuates IL-10 signaling in the LHb, consequently impairing GABAergic function and leading to neuronal hyperactivity, thereby susceptibility to depressive behavior in mice.

In conclusion, our study emphasizes the importance of IL-10 signaling and GABAergic interaction in the LHb as a crucial target for modulating depressive susceptibility due to repeated MS. This provides a novel molecular mechanism for comprehending LHb hyperactivity in ELS-induced depression and insights into the therapeutic potential of IL-10 for adolescent depression.

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