Early Maternal and Social Deprivation Expands Neural Stem Cell Population Size and Reduces Hippocampus/Amygdala-Dependent Fear Memory.

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論 文 内 容 要 旨

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学位論文題目	Early maternal and social deprivation expands neural stem cell population size and reduces hippocampus/amygdala-dependent fear memory (早期母子および社会分離は神経幹細胞のポピュレーションサイズを増加させ、海馬/扁桃体依存性恐怖記憶を減少させる)		

Background and purpose:

Environmental manipulation during postnatal life predisposes the mammalian brain to altered function and cellular remodeling, resulting in behavioral and mood changes. One of the cellular mechanisms contributing to these alterations is adult neurogenesis, which occurs in two neurogenic regions, the olfactory bulb and the dentate gyrus of the hippocampus. Early life stress can exert detrimental or beneficial effects on neural development and postnatal behavior depending on the timing, duration, strength, and ability to control the stressors. During the first two weeks of life in rodents, the hypothalamus-pituitary-adrenal (HPA) axis is insensitive to environmental stimuli and this stress-hyporesponsive period (SHRP) is thought to be neuroprotective against the stress-induced excessive release of corticosterone during early postnatal development. However, it remains unclear whether early life stress alters the size of the neural precursor population and the adult neurogenesis in brain regions that can predict stress-resilience or vulnerability related to emotion and mood, in addition to the classic neurogenic regions. In this study, we focused on maternal and social deprivation (MSD) during the SHRP and investigated how the altered neural stem cell (NSC) population size and adult neurogenesis by this early life MSD affects the emotional behavior and stress response in adulthood.

Methods

We isolated each pup from its dam and littermates between postnatal day P1-14 (early-MSD), P15-P21 (late-MSD), or P1-P21 (extended-MSD). The bodyweight of the pup was measured, and a colony-forming neurosphere assay was performed in a low cell-density culture condition at a 6- and 21-week age. For the corticosterone assay, blood was collected at the end of separation on P14 for the early-MSD group and on P21 for the early-, late- and extended-MSD groups. To estimate the total number of proliferating cells, 5-Ethynyl-2'-deoxyuridine (EdU) short-term labeling was injected at P14 and sacrificed after 2 hours labeling. The estimation of total number of neural precursor cells population was determined by 5-Bromo-2'-deoxyuridine (BrdU) long-term labeling at P15 and sacrificed at 8 week age. Immunohistochemistry staining was performed to estimate the total numbers of EdU^+ cells in the subependymal zone (SEZ) and subgranular zone (SGZ) or $BrdU^+$ cells either co-expressed with $NeuN^+$ or $GFAP^+S100\beta^-$ in

（備考）１．論文内容要旨は、研究の目的・方法・結果・考察・結論の順に記載し、２千字程度でタイプ等を用いて印字すること。

２．※印の欄には記入しないこと。

the SEZ, dentate gyrus (DG) and basolateral amygdala (BLA) by the optical dissector method in every eighth section for the whole brain. The behavioral batteries such as the open field test, fear conditioning test, and Barnes maze was performed to determine the association between the adult neurogenesis and mood changes in MSD mice.

Results and discussion:

In the present study, we show for the first time that early life stress exhibits distinct effects on the activity of the NSC-neurogenesis system in the adult brain, depending on the timing and duration of the stress. MSD during the SHRP increases the size of the NSC population compared to controls; however, the same stress extended beyond the SHRP has the opposite effects. We presented two lines of evidence for the expansion of the NSC population after early-MSD: the estimated number of total NSCs using the neurosphere assay and the BrdU label retention assay in the SEZ. In the DG of the hippocampus, the estimation of NSCs pool was analyzed by BrdU long-term labeling co-expressed with GFAP and negative for S100ß in the SGZ at 8 weeks. Early-MSD enhanced neurogenesis not only in the dentate gyrus of the hippocampus, one of the classic neurogenic regions, but also in the amygdala. This is the first report showing that early life stress during the SHRP enhances amygdalar neurogenesis. In addition, mice exposed to early-MSD exhibited a reduction in amygdala/hippocampus-dependent fear memory.

Conclusion

The results suggest that animals exposed to early life stress during the stress-hyporesponsive period have reinforced stress resilience to cope with perceived stressors to maintain a normal homeostatic state.

別紙様式８（課程博士・論文博士共用）

学位論文審査の結果の要旨

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（学位論文審査の結果の要旨）※明朝体１１ポイント、６００字以内で作成のこと

本論文では、新生マウスを母親及び同胞から一定時間引き離すストレス（maternal and social deprivation: 以下 MSD と示す）を与え、MSD の神経新生及び恐怖記憶への影響を調べた。その結果以下の点を明らかにした。

１） 出生早期の MSD（early-MSD）では脳室下帯において神経幹細胞が増加し、出生後間を置いた後の MSD（late-MSD）や長い期間の MSD(expanded-MSD)ではこうした変化が認められなかった。
２） early-MSD では他の群に比べコルチコステロン分泌が少なかった。この現象は神経保護的と考えられ、将来の神経幹細胞の増加に関連する可能性が考えられた。
３） early-MSD では海馬歯状回と扁桃体で神経新生の増加を認めた。扁桃体での現象はこれまであまり注目されていない。
４） early-MSD は扁桃体/海馬依存性に形成された恐怖記憶からの回復が良好なことが見いだされ、扁桃体での神経新生の関与が推定されたが未解明な部分が多く今後の検討が必要である。

本論文では新生仔期のストレスはタイミングによりストレス耐性の強化に寄与すること、その現象には神経新生が関与することが示され、恐怖記憶のマネジメントに有益な情報をもたらした。また最終試験として論文内容に関した試問を施行し合格と判断されたので、博士（医学）の学位論文に値するものと認められた。

（総字数　598 字）

（令和　2 年　8 月　26 日）