Stress in early life inhibits neurogenesis in adulthood

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Both structure and function of the hippocampus are altered by stress: by increasing levels of corticosteroids, stress causes atrophy of CA3 pyramidal cell dendrites, inhibits adult neurogenesis in the dentate gyrus, and impairs hippocampus-dependent learning. A recent study shows that adverse experience limited to early life, specifically removal of rat pups from their mother for three hours each day, decreases production of new granule neurons in adulthood through a corticosteroid-dependent mechanism. This finding suggests that stress in early life could permanently impair hippocampus-dependent learning and memory and increase susceptibility to depression by inhibiting adult neurogenesis in the hippocampus.

Introduction

Unlike most neurons in the brain, granule cells in the dentate gyrus, part of the hippocampus, continue to be produced during adulthood. Although the specific function of the new granule neurons is not yet clear, their location in the hippocampus suggests that they have a role in learning and memory, and a small number of studies support this idea [1,2]. A growing number of correlations suggest that inhibition of adult neurogenesis in the dentate gyrus might also have a role in depressive illness [3]. First, several different antidepressant treatments increase proliferation of granule cell precursors with a delay paralleling improvement of clinical symptoms [4–7]. Irradiating the rodent hippocampus impairs adult neurogenesis and also prevents antidepressant-induced changes in behavior [8]. Second, stress, acting through corticosteroid stress hormones, inhibits adult neurogenesis in the dentate gyrus [9–11] and is also linked to depression – that is, stress can trigger depressive episodes, and a large subset of people with depressive illness show corticosteroid dysregulation [3,12,13].

Corticosteroids strongly inhibit granule cell precursor proliferation within three hours of corticosterone injection and possibly even sooner [9,14]. Because external stimuli alter corticosteroid levels within a few minutes, environmental changes could cause several fluctuations in the granule cell production rate in a single day. A recent paper by Mirescu *et al.* [15], however, shows that stressful experience during postnatal development also regulates granule cell precursor proliferation on a completely different timescale. When rat pups were removed from their mothers for three hours each day between postnatal day (P)1 and P14, they showed decreased proliferation of granule cell precursors many weeks later, as adults. In other words, stress in early life can permanently affect neurogenesis.

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How does maternal deprivation inhibit neurogenesis?

The maternal deprivation paradigm used by Mirescu *et al.* [15] might seem fairly mild, because each separation lasts only three hours and pups are kept warm in an incubator with home-cage bedding material and littermates. However, this manipulation is stressful enough to increase corticosteroid levels in the pups even though they are generally 'stress hyporesponsive' at this age [16]. In addition to the acute rise in corticosterone levels, this deprivation paradigm has been shown to cause persistent changes in the hypothalamic–pituitary–adrenal (HPA) axis: release of corticosterone in response to mild stress in adulthood is heightened and prolonged in rats that were maternally deprived as pups [17]. This diminished reactive feedback appears to be caused by decreased expression of glucocorticoid receptors relative to mineralocorticoid receptors within the hippocampus, which in turn might be caused by long-lasting epigenetic changes in glucocorticoid receptor DNA [18,19].

Mirescu *et al.* showed that corticosteroids mediate the maternal-deprivation-induced inhibition of adult neurogenesis: they demonstrated that adrenalectomy with corticosterone replacement in adulthood, to fix corticosteroids at a low level, eliminates the difference in cell proliferation (Figure 1). Interestingly, without adrenalectomy baseline corticosterone levels were no different in maternally deprived rats and control rats, despite their different proliferation rates. Additionally in this study, acute predator odor stress increased corticosterone to equivalent levels in both groups and resulted in equivalent proliferation rates (Figure 1).

These effects could result from increased sensitivity of granule cell precursors to corticosteroids in maternally deprived rats. That is, a given level of corticosterone might inhibit proliferation more in deprived rats than in controls. If so, this suggests that the sensitivity of cell proliferation to corticosteroids can be uncoupled from sensitivity of the HPA axis to corticosteroids, because negative feedback appears to be either less sensitive or unchanged [15,18], but not more sensitive, following maternal deprivation. Alternatively, the control of cell proliferation in maternally deprived adult rats might be normal, but corticosterone release might be increased in response to minor stress such as airpuff startle or the

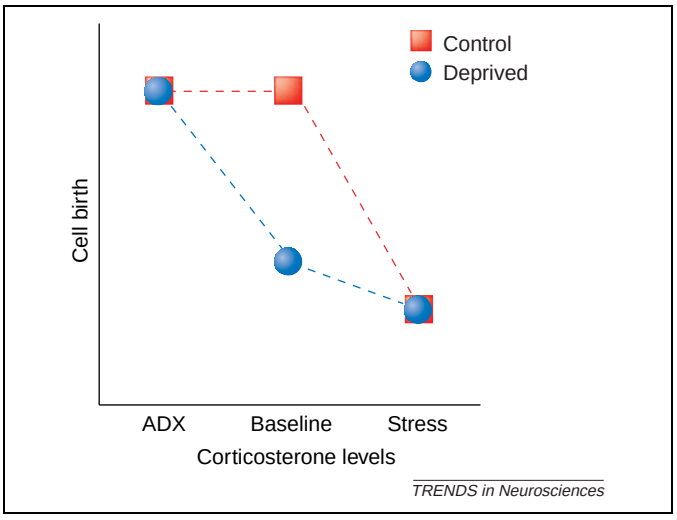

Figure 1. Schematic summary of the effects of maternal deprivation during development on cell proliferation in the adult dentate gyrus, under different stress and corticosteroid conditions (using data from Ref. [15]). Under conditions of low fixed corticosterone levels, produced by adrenalectomy with low-level corticosterone replacement (ADX), the number of dividing cells labeled with BrdU is identical in adult rats that were maternally deprived as pups (blue circles) and normally-reared rats (red squares). Under baseline conditions, proliferation is significantly inhibited in maternally deprived rats. Following a strong stressor such as exposure to predator odor, both groups of rats have similar low levels of proliferation, possibly representing maximal inhibition of neurogenesis achievable by corticosterone. Taken together, these findings suggest that stressful events during development increase sensitivity to stress and/or stress hormones, such that moderate levels of corticosterone or mild stressors produce inhibition of adult neurogenesis seen in control rats only after severe stress.

bromodeoxyuridine (BrdU) injection needed to label dividing cells [11,17,20]. Stronger corticosterone response to predator stress (i.e. to fox odor) was not observed in maternally deprived rats by Mirescu *et al.* [15], but this could be explained by a ceiling effect – that is, this strong stressor might have evoked the maximum possible acute corticosterone release in both deprived and control rats [21,22]. In either case, the findings underscore the complexity of corticosteroid regulation and provide a clear demonstration that corticosterone measurement at a single time point after a single type of stressor is not enough to give a complete picture of effects on the HPA axis. Without the adrenalectomy experiment performed by Mirescu *et al.* [15], the most straightforward – yet incorrect – conclusion from comparing cell proliferation rates and corticosterone levels would be that corticosteroids are not involved in the effects of maternal deprivation on adult neurogenesis.

Concluding remarks

The findings described here show that experiences in early life can permanently alter the sensitivity of adult neurogenesis in the dentate gyrus to stress and/or stress hormones. Further studies will be needed to understand exactly how and where in the HPA axis or hippocampus this change in sensitivity occurs. But wherever it occurs, the resulting inhibition of adult neurogenesis indicates that early life events have a long-lasting effect on the cellular composition of the hippocampus, and possibly also learning and memory processing, in adulthood. Additionally, because stressful events in childhood are known to increase susceptibility to depressive illness in adulthood [23], this persisting inhibition of granule cell birth also adds an important new link between stress, adult neurogenesis and depression.

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0166-2236/$ - see front matter. Published by Elsevier Ltd.
doi:10.1016/j.tins.2005.01.009