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Serotonin and Hippocampal Neurogenesis

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The dentate gyrus continues to produce new granule neurons well into adulthood. This has been demonstrated for many mammalian species, from rodents to primates. The proliferation of granule cell precursors can be suppressed by stressful experiences, presumably via adrenal steroids. Recent evidence suggests that serotonin can enhance the production of new neurons via activation of the 5HT1A receptor. These results present the possibility that the inhibitory effects of stress on granule cell production may be prevented by 5HT1A receptor agonists.
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The role of the molecule serotonin, or 5-hydroxytryptamine, in neurotransmission has been recognized for decades. More recent studies have explored the possibility that serotonin may have structural effects on the brain both during development and in adulthood (Mazer et al. 1997; Yan et al. 1997; Watanabe et al. 1992). These studies have predominantly focused on the role of serotonin in mediating the structure of the adult brain. Our recent studies have identified a new role for serotonin in mediating the structure of the adult brain. We have found that neurogenesis in the adult mammalian dentate gyrus is enhanced by activation of serotonergic receptors (Jacobs et al. 1998).

THE PRODUCTION OF HIPPOCAMPAL GRANULE NEURONS CONTINUES INTO ADULTHOOD

In the majority of mammalian brain regions, the production, migration and death of neurons are restricted to gestation and are complete within several days. Once this developmental phase ends, neurons differentiate and these processes do not continue. In contrast, the granule cell layer (gcl) of the dentate gyrus is formed during an extended period that begins during gestation and continues into adulthood. During the embryonic period, granule cell precursors originate from the wall of the lateral ventricles and migrate along radial glial fibers to the developing hippocampus (Rickmann et al. 1987; Schlessinger et al. 1975; Altman and Bayer 1990a, b). Many of these cells die while migrating toward the forming dentate gyrus (Gould 1994). From the late embryonic period through the first postnatal week in the rat, granule neurons are produced from a pool of precursor cells in the hilus which divide and migrate along radial glia that extend from the hilus to the developing gcl (Schlessinger et al. 1975; Altman and Bayer 1990a, 1990b; Rickmann et al. 1987). This period of time is marked by production of the majority of granule cells as well as by massive cell death (Schlessinger et al. 1975; Gould et al. 1991).

In adulthood, granule cells originate from precursor cells that reside primarily in the subgranular zone (sgz), the region between the gcl and hilus (Cameron et al. 1993a). We and others have demonstrated that these precursor cells divide and produce daughter cells that differentiate into granule neurons. These cells become incorporated into the gcl and express markers of mature granule neurons, including neuron specific enolase

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(NSE), the calcium binding protein calbindin, the NMDA receptor subunit NR1, and Neuronal Nuclei (NeuN): within 3 weeks of DNA synthesis (Cameron et al. 1993a, 1993b; Okano et al. 1993; Kuhn et al. 1996). Cells produced in adulthood receive synaptic input and extend axons into the mossy fiber pathway (Kaplan and Hinds 1977; Kaplan and Bell 1984; Stanfield and Trice 1988). Recent studies have shown that this phenomenon is common to many species of mammals. Three shrews, marmosets, macaques, and humans have been shown to produce a substantial number of new hippocampal neurons in adulthood (Gould et al. 1997, 1998, 1999b).

Recent studies performed using the thymidine analog bromodeoxyuridine to label proliferating cells, and stereological methods of data analysis have shown that thousands of new cells are produced each day in the dentate gyrus of young and middle-aged adults (Gould et al. 1997, 1998, 1999b). The majority of these cells differentiate into mature neurons (Gould et al. 1997, 1998). In the aged animal, however, the production of new granule neurons diminishes significantly in both the rodent and primate (Kuhn et al. 1996; Gould et al. 1999a).

The substantial number of new granule neurons produced in the adult hippocampal formation and the conservation of this process across mammalian evolution strongly suggests a function for adult-generated neurons. One approach to determining the function of these new neurons is to identify the factors and conditions that regulate their occurrence.

STRESS SUPPRESSES THE PRODUCTION OF HIPPOCAMPAL GRANULE NEURONS: POSSIBLE ROLE OF ADRENAL STEROIDS AND NMDA RECEPTOR-MEDIATED EXCITATORY INPUT

We have shown that stressful experiences suppress the production of new hippocampal granule neurons in three mammalian species. First, exposure of developing and adult rats to the odors of natural predators, resulted in a significant decrease in the number of hippocampal cells incorporating 3H-thymidine or bromodeoxyuridine in the dentate gyrus (Gould and Cameron 1996; Tanapat et al. 1998). Second, exposure of adult marmosets to resident-intruder stress resulted in a similar effect, diminished production of new hippocampal neurons (Gould et al. 1998). Third, the experience of subordination stress suppresses the formation of new cells in the dentate gyrus of adult tree shrews (Gould et al. 1997). This effect is not transient but rather persists throughout a period of chronic stress as well. Twenty-eight days of daily exposure (1 hr) to a dominant tree shrew resulted in a persistent reduction in the number of new granule cells produced (Fuchs et al. 1997). This chronic stress paradigm was associated with a decrease in the volume of the gcl (Fuchs et al. 1997) indicating that a lasting suppression in the addition of new neurons may alter the structure of the dentate gyrus. Because all of these paradigms elevate levels of circulating adrenal steroids, it is possible that the suppressive effects on granule cell production were mediated through activation of the hypothalamic-pituitary-adrenal axis.

Indeed, several lines of evidence indicate that circulating levels of adrenal steroids modulate the production of granule neurons. First, levels of adrenal steroids correlate negatively with the rate of granule cell production. During the first two postnatal weeks in the rat, termed the stress hyporesponsive period, the levels of adrenal steroids are low and the rate of granule cell production is high (Sapolsky and Meaney 1986; Schlessinger et al. 1975). In adulthood, the basal levels of adrenal steroids are relatively high and the rate of granule cell production is relatively low (Gould 1994). Second, we have found that experimental increases in the levels of adrenal steroids result in significant decreases in the rate of granule cell production during development (Gould et al. 1991) and in adulthood (Cameron and Gould 1994). Third, we have found that removal of adrenal steroids stimulates the proliferation of granule cell precursors (Gould et al. 1992), the vast majority of which differentiate into neurons (Cameron and Gould 1994). Collectively, these findings indicate that adrenal steroids naturally suppress the production of granule neurons. However, very few precursor cells in the developing or adult dentate gyrus express either the Type 1 (mineralocorticoid) or Type 2 (glucocorticoid) receptor (Cameron et al. 1993) suggesting that adrenal steroids influence granule cell production indirectly through another factor.

Considerable evidence indicates that adrenal steroids suppress granule cell production by acting through an NMDA receptor-mediated pathway (Cameron et al. 1998). It is likely that these changes in granule cell genesis as a result of pharmacological manipulations of NMDA receptors reflect a natural inhibition of this process by perforant path input because lesion of the entorhinal cortex results in a significant increase in the number of proliferating cells in the dentate gyrus (Cameron et al. 1995). However, our preliminary results indicate that precursor cells do not express the NMDA receptor subunit NR1 (Cameron and Gould 1996), an essential subunit of functional NMDA receptors (Luo et al. 1997), suggesting that NMDA receptor-mediated excitatory input influences granule cell genesis indirectly through an as yet undetermined factor. To date, the factors that directly mediate granule cell production remain undetermined.

POTENTIAL CANDIDATES FOR FACTORS THAT DIRECTLY REGULATE GRANULE CELL GENESIS: GROWTH FACTORS AND SEROTONIN

Peptide growth factors have been shown to stimulate mitosis in a variety of different systems. In particular, epidermal growth factor (EGF) and transforming growth factor (TGFα), the endogenous ligand for the EGF receptor in brain, have been shown to act as potent mitogens in a variety of systems (Anchan et al. 1991; Farbman and Bucholz 1996; Yamashita and Oesterle 1995; Zheng et al. 1997). Recent evidence indicates that a significant percentage of the precursor population in the adult dentate gyrus expresses EGF receptors (EGFr) (Okano et al. 1996). Moreover, TFGα is produced at relatively high levels in the adult dentate gyrus and appears to be synthesized by neurons (Wilcox and Derynck 1988; Seroogy et al. 1991). These findings present the possibility that EGF or TGFα is the endogenous factor that directly stimulates the proliferation of granule cell precursors. Recently, we have found that activation of EGFr, by infusion of EGF or TGFα directly into the dentate gyrus, stimulates the proliferation of granule cell precursors (Tanapat and Gould 1997).

SEROTONIN

Another potential candidate for the direct mediator of granule cell genesis is the neurotransmitter serotonin or 5-hydroxytryptamine (5-HT). Serotonin has been shown to stimulate cell proliferation in nonneuronal systems (Fanburg and Lee 1997; Takuwa et al. 1989). The dentate gyrus is enriched with 5HT1A receptors (Azmitia et al. 1996): and receives serotonergic innervation from the median raphe nucleus of the brainstem (Patel et al. 1996).

A considerable body of evidence suggests that 5HT may stimulate the production of neurons in the dentate gyrus. First, conditions that are associated with diminished granule cell genesis, such as malnutrition (Debassio et al. 1996), aging (Kuhn et al. 1996; Gould et al. 1999), high corticosterone (Cameron and Gould 1994), stress (Gould et al. 1997, 1998), and NMDA receptor activation (Cameron et al. 1995), also decrease the density of 5HT fibers or 5HT1A receptors, or inhibit the release of 5HT in the dentate gyrus (Blatt et al. 1994; Chalmers et al. 1993; McKittrick et al. 1995; Nishimura et al. 1995; Meijer and deKloet 1994; Watanabe et al. 1993; Tao and Auerbach 1996; Whitton et al. 1994; Nyakas et al. 1997). Second, experimental manipulations that stimulate granule cell genesis, such as seizures (Parent et al. 1997), adrenalectomy (Cameron and Gould 1994), and NMDA receptor antagonist treatment (Cameron et al. 1995), also increase the density of 5HT1A receptors or the release of 5HT in the dentate gyrus (Hayakawa et al. 1994; Burnet et al. 1995; Whitton et al. 1994; Kuroda et al. 1994). Third, our preliminary evidence indicates that pharmacological manipulations that elevate 5HT levels in the hippocampus (fenfluramine) or stimulate 5TH1A receptors (8-OH-DPAT) increase the rate of proliferation of granule cell precursors (Jacobs et al. 1998). The majority of these cells differentiate into granule neurons (unpublished observations). It is likely that the stimulatory effect of 5HT on proliferating cells in the dentate gyrus is not due to an effect of these drugs on adrenal steroids, as drugs which elevate 5HT levels typically increase the levels of circulating corticosterone (Serri and Rasio 1987; Baudrie et al. 1993), a condition that suppresses granule cell genesis (Cameron and Gould 1994). However, it is possible that 5HT acts downstream of adrenal steroids and NMDA receptors, as NMDA receptor antagonist treatment stimulates the release of 5HT in the brain (Kondoh et al. 1994; Whitton et al. 1994).

Evidence from nonneural systems indicates that EGF and 5HT can exert additive or synergistic actions on cell proliferation (Varrault et al. 1992; Takuwa et al. 1989). Collectively, these data present the possibility that the production of new granule neurons is directly stimulated by activation of EGF or 5HT1A receptors located on granule cell precursors and may be a critical step in the final common pathway in the regulation of this process. Conversely, stress may inhibit granule cell production by activating a pathway that involves glucorticoids, NMDA receptor-mediated excitatory input and ultimately decreases the availability of serotonin or its receptors (Figure 1). Although rapid decreases in the density of hippocampal 5HT1A receptors have been observed following stress, it is interesting to note that different types of stressors have varying effects on 5HT release in the hippocampus (Kirby et al. 1997). Our studies have focused on a small number of species-relevant stressors, all of which inhibit cell proliferation in an acute manner (Gould et al. 1997, 1998; Tanapat et al. 1998). It is possible that other stressors would have different, or no, effects on granule cell production depending on their influence on serotonergic systems. For example, comparison of stressors that stimulate hippocampal serotonin release with those that do not but that downregulate 5HT1A receptors would be particularly instructive.

FUNCTIONAL SIGNIFICANCE OF ADULT-GENERATED HIPPOCAMPAL NEURONS

The persistence of hippocampal neurogenesis in adulthood raises the important question of what the func-

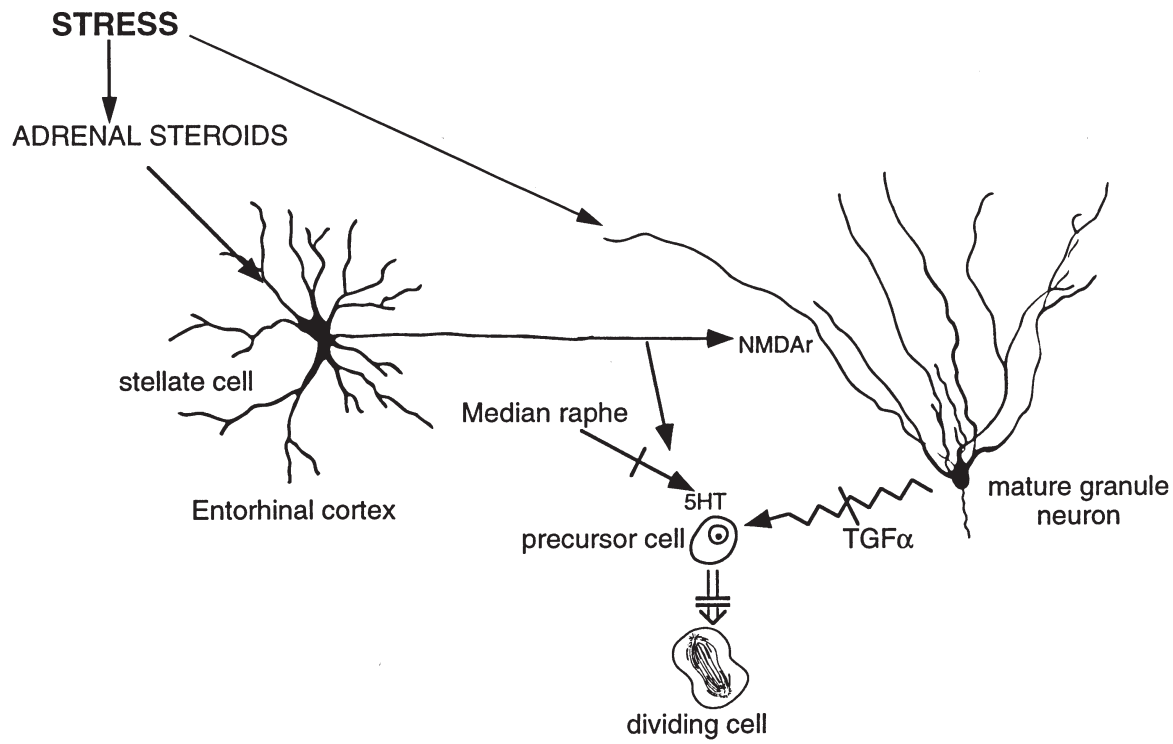

Figure 1. Schematic model demonstrating a possible pathway that regulates stress-induced suppression of granule cell genesis. Stress may have multiple actions on factors that influence cell proliferation, including to increase the levels of circulating adrenal steroids and stimulate glutamate release thus activating NMDA receptors. Activation of this pathway may inhibit two potential mitogenic systems; transforming growth factor alpha and serotonin. Stress may ultimately prevent the release of TGFα from granule neurons and diminish the impact of serotonin by downregulating 5HT1A receptors on granule cell precursors. Under conditions of no stress, both TGFα and serotonin may stimulate granule cell production.

tional significance of adult-generated cells might be. The role of the hippocampal formation in learning and memory has been recognized for decades (Squire and Zola 1996) but the cellular mechanisms that underlie this association remain elusive. Our findings suggest that adult-generated cells are specifically affected by, and possibly involved in, learning and memory (Gould et al. 1999). Stress-induced suppression of neurogenesis may underlie deficits in learning and memory reported following chronic corticosterone treatment or stress (Bodnoff et al. 1995; Krugers et al. 1997). The extent to which such functional deficits can be prevented by drugs that stimulate granule cell production, e.g., serotonergic agonists, remains undetermined.

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