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Glucocorticoids and the Hippocampus

Developmental Interactions Facilitating the Expression of Behavioral Inhibition

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Abstract

When threatened, the rapid induction of fear and anxiety responses is adaptive. This article summarizes the current knowledge of the neurobiological development of behavioral inhibition, a prominent response occurring in fear and anxiety-provoking situations. In the rat, behavioral inhibition as exemplified by freezing first appears near the end of the second postnatal week. This emergence of freezing coincides with the developmental period marked by the rapid increase in plasma concentrations of glucocorticoids. Studies show that removal of glucocorticoids at this time severely impairs the age-dependent appearance of freezing. This behavioral impairment produced by adrenalectomy, however, is prevented by exogenous glucocorticoid administration. The effectiveness of glucocorticoids in facilitating the development of freezing appears to be caused by its actions in the hippocampus. In particular, glucocorticoids appear to play a vital role in the postnatal cellular development of the hippocampal dentate gyrus. Doses of glucocorticoids shown to reverse the behavioral inhibitory deficits occurring after adrenalectomy are ineffective when hippocampal dentate granule neurons are destroyed by neurotoxins. Notably, site-specific administration of glucocorticoids to the dorsal hippocampus is successful in promoting the occurrence of freezing in the adrenalectomized rat pup. It is hypothesized that glucocorticoids exert their behavioral inhibitory effects by influencing the development of the septohippocampal cholinergic system. Support for this hypothesis is derived from work demonstrating the importance of glucocorticoids on nerve growth factor systems that play a critical role in septohippocampal cholinergic survival.

Index Entries: Behavioral inhibition; freezing; emotional development; fear; glucocorticoids; corticosterone; hippocampus; dentate gyrus; neurotrophic factors; nerve growth factor; septohippocampal cholinergic system.

Introduction

The ability to suppress ongoing patterns of behavior and assume a motionless or immobile posture when threatened is a characteristic observed in diverse species. This behavioral inhibitory response that is often characterized as freezing varies widely in its developmental appearance across species. In addition, individuals within a species differ in their propensity to freeze (reviewed by Gray, 1987; Boissy, 1995). These behavioral differences emerge from an early age and appear to be a stable trait of the individual (Stevenson-Hinde, 1983; Kagen and Snidman, 1991; Boissy, 1995). Variation in the expression of behavioral inhibition suggests that mechanisms regulating fear and anxiety differ among individuals. From a clinical standpoint, differences in temperament have important implications for the development of psychiatric disorders. Of potential relevance are studies suggesting that children exhibiting extreme behavioral inhibition to the unfamiliar are vulnerable to develop anxiety disorders (Rosenbaum et al., 1988; Biederman et al., 1990).

There is a considerable body of research conducted using adult rodents that examined the neural and pharmacological bases of freezing (*see* reviews by Blanchard and Blanchard, 1988; Panksepp et al., 1991; Davis, 1992; LeDoux, 1992). These investigations have implicated various brain regions, including the amygdala, hippocampus, and the central gray, in the control of freezing. Neurochemical systems implicated in the modulation of freezing include, but are not limited to, monoamines, GABA/benzodiazepine, and opiate systems.

In contrast, information on the developmental neurobiology of freezing is scarce. A developmental neurobiological approach to the study of behavioral inhibition, however, may yield important insights into how diverse brain nuclei and neurochemical systems begin to act in concert to regulate freezing. Equally important, research suggests that early developmental events exert a profound influence on setting the emotional tone of the individual. For example, exposure of young rodents to human handling or an enriched environment produces a reduction in fear behavior, facilitates learning, alters the regulation of the hypothalamic-pituitary–adrenal stress hormone system, and influences the development of brain structures, such as the hippocampus (HC) (Gray, 1987; Renner and Rosenzweig, 1987).

This article reviews data emphasizing the role of glucocorticoids and the HC in relation to the development of behavioral inhibition. In addition, an outline is introduced for future examination of neurobiological hypotheses relevant to the developmental regulation of behavioral inhibition. It should be stated that throughout this article the term behavioral inhibition refers specifically to freezing, and not to withdrawal or avoidance tendencies or to the suppression of appetitive behavior as used by other investigators (e.g., Gray, 1982). However, the ideas expressed in this article may have implications for the manifestation of these other patterns of behavior.

Glucocorticoids and the Developing Hippocampus

The HC is implicated in cognitive functions related to learning and memory (O'Keefe and Nadel, 1978; Squire and Zola Morgan, 1991). The HC also represents a useful in vitro model to examine mechanisms underlying synaptic plasticity, especially long-term potentiation and long-term depression (Bliss and Collingridge, 1993; Kirkwood et al., 1993). This latter work suggests that the HC may have a critical role in experience-dependent synaptic modification of behavior.

In respect to development, the majority of HC dentate granule cells are established during the early postnatal period (Altman and Das, 1965; Schlessinger et al., 1975; Bayer, 1980a,b; Cowan et al., 1980). In the first postnatal week, over 80% of dentate granule cells are formed. Neurogenesis of dentate cells occurs in the hilus, from which they migrate to the granule cell layer (Schlessinger et al., 1975;

Rickmann et al., 1987). This early postnatal period also coincides with the period of marked HC granule cell death (Gould et al., 1991a). It is estimated that only 5–10% of granule cells are formed after postnatal d 18 (Bayer 1980b).

The HC is a prominent target site for adrenal steroids (Stumpf, 1971; Gerlach and McEwen, 1972). Both mineralocorticoid and glucocorticoid receptors are present and bind corticosterone (CORT), the major glucocorticoid of the rat, although with different affinities (Reul and DeKloet, 1985; McEwen et al., 1986; De Kloet, 1991). Binding of adrenal steroids to their intracellular receptors results in activation or transformation of the hormone–receptor complex into a DNA-binding protein that is translocated to the nucleus (Walters, 1985). The steroid–receptor complex then binds to DNA sequences resulting in transcriptional effects. One major genomic effect induced by HC adrenal steroid–receptor activation is the regulation of glucocorticoid negative feedback (McEwen et al., 1986; Dallman et al., 1987; Jacobson and Sapolsky, 1991).

In the first postnatal week, mineralocorticoid and glucocorticoid receptors are present in the HC (Rosenfeld et al., 1988a,b, 1990; Sarrieau et al., 1988). Although both receptor types may be coexpressed in dentate gyrus and pyramidal neurons, the density of these receptor types differs throughout the HC (Reul and De Kloet, 1985, 1986; Lawson et al., 1991; van Eekelen et al., 1991; Bohn et al., 1994). *In situ* hybridization and RNase protection assay studies reveal that mineralocorticoid receptor mRNA is expressed primarily in HC granule and pyramidal cells. Glucocorticoid receptor mRNA is found predominantly in pyramidal cells located in the CA1 field of Ammon's horn, but at lower levels in CA3 and in the hilar region. In addition, throughout the HC, mineralocorticoid receptor mRNA appears to be expressed at higher levels than glucocorticoid receptor mRNA.

Shortly after birth in the rat, basal concentrations of plasma CORT are reduced and do not increase until the end of the second postnatal week (Henning, 1978; Sapolsky and Meaney, 1986). During this period, HC dentate gyrus cell genesis and cell death are reported to be regulated by corticosteroids (Gould et al., 1991b,c). Administration of either exogenous CORT or aldosterone during the first postnatal week increases the density of pyknotic cells in the hilus. In addition, the appearance of pyknotic cells decreases in the dentate granule layer. Importantly, adrenalectomy procedures conducted at the end of the second postnatal week, when endogenous CORT levels begin to increase, produce an elevation in the density of pyknotic cells throughout the hilus and dentate granule layer. These results implicate endogenous corticosteroids in playing an important role in HC dentate gyrus development.

The development of HC dentate granule cell connections has been described. The perforant pathway, the major afferent connection, arises from the entorhinal cortex and terminates in the molecular layer of the dentate gyrus (Raisman et al., 1965; Steward, 1976; Wyss, 1981). Additional input fibers, i.e., associational and commissural connections, to the dentate gyrus project from cells located in the ipsilateral and contralateral hilus (Blackstead, 1956, Zimmer, 1971; Gottlieb and Cowan, 1973; Hjorth-Simonsen and Laurberg, 1977; Fricke and Cowan, 1978). Locus ceruleus noradrenergic (Blackstead et al., 1967; Moore and Bloom, 1979), raphe nuclei serotonergic (Moore and Halaris, 1975; Kohler and Steinbusch, 1982), and septal/diagonal band cholinergic fibers (Lewis and Schutz, 1967; Swanson and Cowan, 1979; Matthews et al., 1987) also innervate the HC dentate gyrus, where they may have trophic functions, such as contributing to the development of target neurons (Lauder, 1987; Meier et al., 1991). Furthermore, neurotransmitter receptors and their actions on target cells change developmentally (Ito and Cherubini, 1991). Output of dentate granule cells occurs via their massive mossy fiber axons, which project to cells in the hilus, and CA2 and CA3 pyramidal cells of the HC (Swanson et al., 1978; Gaarskjaer, 1986). The distribution and appearance of entorhinal afferents to the molecular layer and mossy fiber terminal projections to

regions of Ammon's horn acquire adult-like characteristics by the conclusion of the second postnatal week (Cowan et al., 1980; Amaral and Dent, 1981). Alterations in glucocorticoid facilitation of HC dentate gyrus cell development during the early postnatal period may critically undermine the establishment of diverse afferent projections, the density of efferent synaptic connections, and their neurochemical, endocrine, and behavioral functions.

Glucocorticoids and the Development of Behavioral Inhibition

The development of behavioral inhibition was characterized in a series of studies in which rat pups, at different preweaning ages, were exposed to an anesthetized conspecific placed on the opposite side of a wire mesh barrier (Takahashi, 1992a,b, 1994a). These developmental studies revealed that freezing first appeared at the end of the second postnatal week (*see also* Collier and Bolles, 1980). At 14 d of age, rat pups exhibited a robust freezing response when exposed to an unfamiliar adult male rat, but not to the nursing dam, a familiar adult male rat, or an unfamiliar juvenile rat. Freezing may facilitate survival when the young rat detects the odor of an unfamiliar and potentially infanticidal adult male rat or predator during excursions from the nest.

Several lines of evidence support the hypothesis that glucocorticoids play a major role in the development of behavioral inhibition. First, endogenous plasma concentrations of CORT increase shortly after the first postnatal week. In the Sprague-Dawley rat that is used to study behavioral inhibition, basal levels of plasma CORT are nearly undetectable before postnatal d 11. However, a greater than threefold elevation in endogenous CORT occurs by 14 d of age (Takahashi and Kim, 1995). Second, preventing the endogenous increase in glucocorticoids by adrenalectomy produces deficits in freezing. That is, d 10 adrenalectomized rats exhibit a reduction in freezing when tested at 14 d of age (Takahashi and Rubin, 1993). Third, this impairment in behavioral inhibition is prevented by exogenous CORT administered throughout the period of adrenalectomy (Takahashi and Rubin, 1993).

Additional support for a developmental effect of glucocorticoids on behavioral inhibition is demonstrated in studies showing that adrenalectomy fails to disrupt freezing when performed after the response is fully developed (Takahashi, 1994b). Rat pups adrenalectomized on postnatal d 14 exhibit freezing at levels comparable to intact control rats when tested for behavioral inhibition on d 18. Furthermore, exogenous CORT is ineffective in reinstating freezing in d-10 adrenalectomized rats when CORT treatment is delayed until d 14 (Takahashi, 1994b).

The behavioral effects of early glucocorticoid removal appear to be long-lasting. In adulthood, rats that were adrenalectomized in early life appear to be less behaviorally inhibited. These early adrenalectomized rats exhibited reduced latencies to leave a start box and high levels of wheel running activity (Yehuda et al., 1988). Recently, we found that in early adulthood, d 10 adrenalectomized rats exhibited less freezing in response to cat fur than control rats (Takahashi and Goh, 1995, unpublished results).

Notably, the behavioral effects of glucocorticoids in the young rat are unlike those produced in adulthood. In adult rats, adrenalectomy may even increase the level of freezing, whereas exogenous glucocorticoid administration reverses the behavioral effects of adrenalectomy (Sakaguchi et al., 1984). This enhancement of freezing in adulthood is hypothesized to stem from putative arousing effects of pituitary adrenocorticotropin, which is elevated after adrenalectomy (Weiss et al., 1970).

In summary, current data support the view that there exists a critical or early period of development when glucocorticoids exert organizing effects on a behavior response associated with fear and anxiety. The developmental effects of glucocorticoids that facilitate the appearance of behavioral inhibition were shown to occur between postnatal d 10 and 14.

It should be noted that in early development, other steroid hormone systems also play a major role in behavioral expression. For example, sex differences result from the perinatal organizing actions of gonadal hormones on the structure and function of the vertebrate brain and periphery (for reviews, *see* Gorski, 1971; Dorner, 1980; Goy and McEwen, 1980; Breedlove, 1992).

Glucocorticoids, the HC, and Behavioral Inhibition

Studies indicate that neurotoxin-induced damage to developing HC dentate granule neurons produces severe behavioral deficits in adrenalectomized rat pups treated with exogenous CORT (Takahashi, 1995). In contrast, rat pups with largely intact HC granule cells, but with cellular damage in the hilar region, are capable of freezing after exogenous CORT administration. Hence, HC dentate granule cells appear to be the important target site for mediating the developmental behavioral effects of CORT. This hypothesis is further strengthened by the demonstration that implantation of CORT-filled cannula into the dorsal HC dentate gyrus is effective in facilitating the display of freezing in the adrenalectomized rat pup (Takahashi, 1995). Taken together, these studies begin to implicate a critical component, viz., HC dentate granule cells, of the behavioral inhibition neural system that is directly influenced by CORT in early life.

Early environmental events may also perturb HC development, resulting in endocrine and behavioral alterations. Rat pups removed daily from the nest and placed in social isolation for a brief period of time over a 3-wk period beginning from the d of birth exhibit increased stress-induced glucocorticoid negative feedback in adulthood (Meaney et al., 1988). Increased negative feedback effects may be caused by an elevation in HC glucocorticoid receptor density and receptor binding. Furthermore, this change in glucocorticoid receptor capacity is induced during a critical developmental period. Only rat pups exposed repeatedly to human handling in the first two postnatal weeks exhibited increased hippocampal glucocorticoid receptor binding capacity (Meaney and Aitken, 1985). Changes in the HC glucocorticoid receptor system occurring in handled rats may lead to some of the behavioral/cognitive effects reported to occur as a function of age (Meaney et al., 1988). These studies, in conjunction with the research on behavioral inhibition, show that HC function can be profoundly altered by early developmental events.

Putative Early Glucocorticoid Effects on Neurotrophic Actions in the HC: Implications for the Development of Behavioral Inhibition

A key question that remains unanswered concerns the underlying basis by which glucocorticoid-induced development of the HC leads to behavioral inhibition expression. However, our recent demonstration (Takahashi and Goh, 1996) showing an involvement of the HC cholinergic system in modulating the occurrence of behavioral inhibition in preweanling rats suggests a possible developmental scenario involving glucocorticoids, neurotrophic factors, and the septohippocampal cholinergic system.

Nerve Growth Factor (NGF) and Brain Cholinergic Development

NGF is an important trophic agent for the peripheral sympathetic and sensory nervous systems (Levi-Montalcini and Angeletti, 1968; Thoenen and Barde, 1980; Longo et al., 1993). NGF mRNA, NGF protein, and its receptors are located in the brain, with especially high levels in the HC and cortex (Korsching et al., 1985; Shelton et al., 1986; Whittemore et al., 1986). In addition to binding to $p75^{NGFR}$, a low-affinity receptor, NGF binds to specific receptors of the *trk* gene protein kinase family resulting in neurotrophic effects (Hempstead et

al., 1991; Kaplan et al., 1991a, 1991b; Klein et al., 1991). NGF is a ligand for *trkA* protein resulting in a functional response, i.e., tyrosine phosphorylation. During development, *trkA* mRNA begins to increase in septum and striatum between postnatal d 7 and 14 and continues until 4 wk of age (Ringstedt et al., 1993). In parallel, NGF mRNA in the HC increases gradually after birth, attains a peak at d 21, and declines thereafter (Large et al., 1986). Within the HC, NGF synthesis occurs predominantly in neurons of the dentate gyrus and HC pyramidal cell layer (Ayer-Leliere et al., 1988; Enfors et al., 1990).

Evidence suggests a physiological role for NGF on the basal forebrain cholinergic system. Both immunohistochemical and *in situ* hybridization studies reveal the existence of $p75^{NGFR}$ in basal cholinergic neurons (Richardson et al., 1986; Buck et al., 1987; Vasquez and Edendal, 1991). Furthermore, in these cholinergic neurons, trkA mRNA is colocalized with $p75^{NGFR}$ mRNA and choline acetyltransferase (ChAT), the enzyme responsible for acethylcholine synthesis. Experimental studies further show that transection of the fimbria, which produces a lesion of septohippocampal cholinergic afferents, results in degeneration of the septal cholinergic cell bodies. These degenerative changes, however, are prevented by intracerebroventricular administration of NGF (Hefti, 1986; Williams et al., 1986; Kromer, 1987; Koliatsos et al., 1991). Both biosynthetic activities and the structural integrity of septohippocampal cholinergic neurons appear to be dependent on NGF. Importantly, septal cholinergic neurons of preweanling rats appear to be especially vulnerable to the loss of HC target regions (Cooper et al., 1993; Sofroniew et al., 1993). This vulnerability may explain the rapid reduction in behavioral inhibition occurring after adrenalectomy in early life.

In rats, NGF may be responsible for promoting septohippocampal cholinergic maturation, which occurs largely in the early postnatal period (Matthews et al., 1974; Nadler et al., 1974; Ben-Barak and Dudai, 1979; Crutcher, 1982; Milner et al., 1983). Studies demonstrate that ChAT levels in the basal forebrain are associated with the rapid appearance of HC NGF and its mRNA between postnatal d 12 and 14 (Large et al., 1986; Auberger et al., 1987). Developmental studies further indicate that exogenous NGF dose-dependently increases the level of cholinergic markers in brain regions, including the septum and HC (Gnahn et al., 1983; Mobley et al., 1986; Kewitz et al., 1990). Conversely, infusion of anti-NGF during development suppresses the expression of *trkA* and ChAT (Li et al., 1995). The accelerated maturation of the cholinergic system by exogenous NGF administration has potential functional implications. For example, administration of exogenous NGF to neonatal mice accelerates their behavioral sensitivity to cholinergic drugs (Calamandrei et al., 1991).

Glucocorticoids Influence Brain NGF Systems

Studies demonstrate that adrenal hormones are capable of regulating NGF synthesis. Administration of either dexamethasone, a synthetic glucocorticoid, or the mineralocorticoid aldosterone increased NGF mRNA levels in HC cell cultures as well as in vivo (Barbany and Persson, 1992; Lindholm et al., 1992). In contrast, adrenalectomy reduces NGF levels in the HC (Aloe, 1989; Barbany and Persson, 1992). Accompanying the decline in HC NGF is a reduction in ChAT-immunoreactive neurons in the septal region. The adrenalectomy-induced effects on NGF and ChAT, however, are reversed by exogenous CORT administration (Aloe, 1989).

Stress-Induced Activation of the Septohippocampal Cholinergic System

In the adult rat HC, studies have found a rapid rise in high-affinity choline uptake and release after exposure to stress (Finkelstein et al., 1985; Gilad et al., 1985). Furthermore, corticosteroids appear to contribute to the release of acetylcholine (Gilad et al., 1987; Imperato et al., 1989). Other investigators reported that

blockade of HC muscarinic receptors with scopolamine augments stress-induced concentrations of plasma corticosterone (Bhatnagar et al., 1994).

Less information is available on the relationship between the developing septohippocampal cholinergic system and early emotional expression (Hess and Blozovski, 1987). However, infusion of oxotremorine, an M_2 muscarinic receptor agonist into the molecular layer of the dorsal HC dentate gyrus was shown recently to decrease the duration of freezing in 14-d-old rat pups (Takahashi and Goh, 1996). In the HC, M_2 autoreceptors are located on presynaptic terminals where oxotremorine acts to reduce cholinergic release (Raiteri et al., 1984; Hoss et al., 1990; Gorman et al., 1994). Presynaptic cholinergic terminals are highly concentrated in the molecular layer of the dentate gyrus (Quirion, 1985). Notably, we also found that HC infusions of oxotremorine did not lead to global changes in the display of other responses that were examined, such as locomotor activity (Takahashi and Goh, 1996).

According to the data summarized in this section, it is conceivable that endogenous glucocorticoids acting via NGF systems in the HC dentate gyrus are ultimately responsible for promoting septohippocampal cholinergic development. Thus, the threat-induced release of acetylcholine from presynaptic terminals in the HC may have a prominent role in mediating the age-dependent facilitation of behavioral inhibition.

Conclusions

The present article describes the developmental neurobiology of behavioral inhibition. The developmental appearance of behavioral inhibition may be the outcome of complex interactions involving glucocorticoids, the HC, NGF, and the septohippocampal cholinergic system (summarized in Fig. 1). The mechanisms involved in mediating these interactions remain to be defined. Furthermore, identification and characterization of other neural input and output pathways to the HC and septum that contribute to the eventual development of freezing require future attention.

Although the current article focuses on the early effects of glucocorticoids on HC development and behavioral inhibition, endogenous glucocorticoids are also known to produce developmental effects in other rat brain regions, such as the cerebellum. For example, after adrenalectomy in early life, there is an increase in brain cell growth and myelination that is evident in adulthood (Devenport and Devenport, 1982; Meyer, 1983; Meyer, 1985; Yehuda and Meyer, 1991). These brain alterations underscore some of the long-term effects of early adrenalectomy. Whether these long-term effects produced by early adrenalectomy eventually contribute to the regulation of behavioral inhibition, are specifically involved in modulating other behavioral patterns, or produce generalized behavioral alterations is a matter for future research to resolve.

Finally, brain cholinergic systems appear to have an important role in modulating arousal and attentional processes (Nilsson et al., 1990; Inglis et al., 1994; Muir et al., 1994; Voytko et al., 1994). These studies show that cholinergic release into the HC and cortex accompanies behavioral activation and stimulus anticipation. Accordingly, it is not altogether difficult to conceive that the alert immobility response that the organism readily exhibits when danger is sensed may require a highly functional septohippocampal cholinergic system for adaptive responding. For example, in order to survive, the organism must effectively detect and avoid the region of the threat and recall the spatial location of appropriate refuge. The hypothesized spatial mapping properties of the HC (O'Keefe and Nadel, 1978) may be rapidly enhanced by threat-induced activation of the septohippocampal cholinergic system. In addition, alterations in brain cholinergic function may be an important contributing factor to differences among individuals in emotional behavior. As a case in point, the WKY strain of rats is reported to have high levels of ChAT in

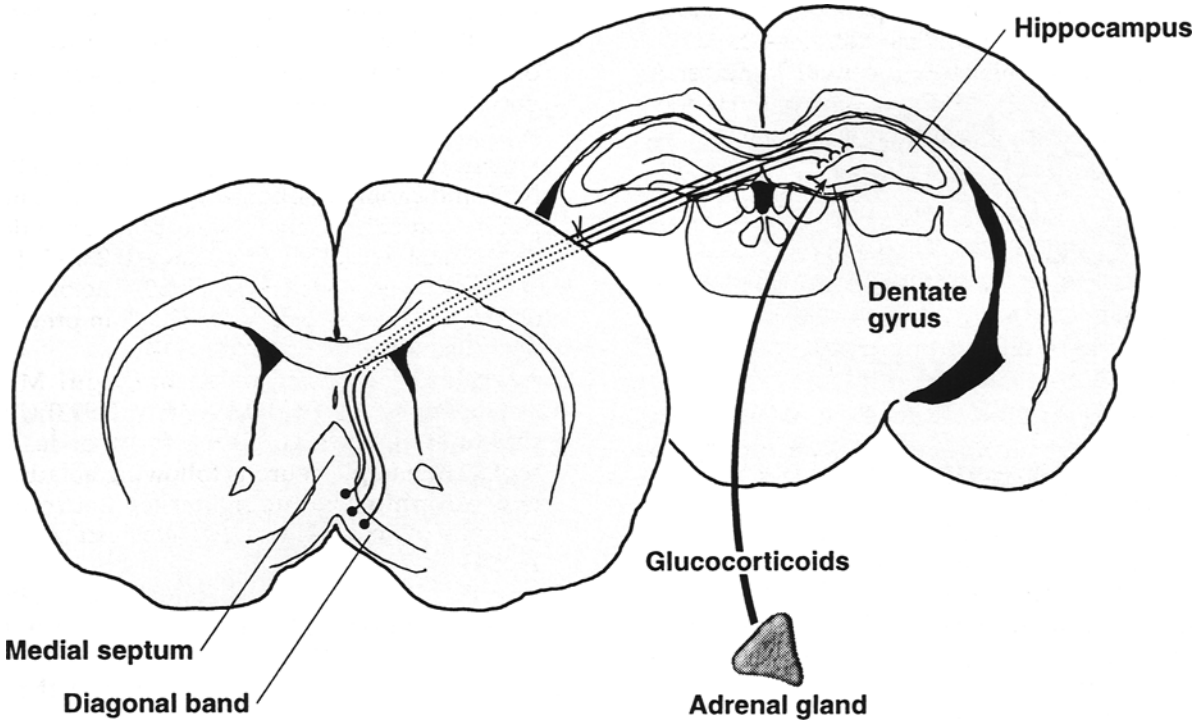

Fig. 1. Schematic developmental model of glucocorticoid effects on the HC dentate gyrus underlying the appearance of behavioral inhibition. The postnatal increase in glucocorticoid secretion by the adrenal gland promotes the development of HC dentate granule neurons. In addition, it is hypothesized that glucocorticoids may have a vital role in regulating HC NGF systems critical for the eventual maturation of cholinergic projections from the medial septum and diagonal band to the dentate gyrus. Septohippocampal cholinergic activation induced by threatening stimuli may play a crucial role in regulating behavioral inhibition development and expression.

the HC (Gilad and Gilad, 1981). Importantly, when stressed, WKY rats engage in prolonged bouts of freezing (Sakaguchi et al., 1984; Pare, 1989). The potential developmental actions of glucocorticoids on the septohippocampal cholinergic system may serve to assist in setting the tone of behavioral inhibition expression by modulating the individual's level of stress-induced arousal and attention.

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