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Plasticity of the Stress Response Early in Life: Mechanisms and Significance

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Abstract

The concept that early-life experience influences the brain long-term has been extensively studied over the past 50 years, whereas genetic factors determine the sequence and levels of expression of specific neuronal genes, this genetic program can be modified enduringly as a result of experience taking place during critical developmental periods. This programming is of major importance because it appears to govern many behavioral and physiological phenotypes and promote susceptibility or resilience to disease. An established example of the consequences of early-life experience-induced programming includes the effects of maternal care, where patterns of augmented care result in decreased neuroendocrine stress responses, improved cognition and resilience to depression in the recipients of this care. Here, we discuss the nature and mechanisms of this programming phenomenon, focusing on work from our lab that was inspired by Seymour Levine and his fundamental contributions to the field.

Keywords

early-life experience; maternal care; handling; corticotropin releasing hormone; CRH; CRF; hypothalamo-pituitary-adrenal axis; programming; stress; resilience; HPA; epigenetics; depression; glucocorticoid receptors

IMPORTANCE OF EARLY-LIFE EXPERIENCE

Long-lasting influence of early-life experience on neuroendocrine and behavioral responses to threatening situations has been suspected in humans, and considered to involve changes in the hypothalamic-pituitary-adrenal (HPA) axis (reviewed in Heim, Plotsky, & Nemeroff, 2004). This influence has been directly demonstrated in experimental animals including rodents (Hess, 1969; Levine & Lewis, 1959; Meaney et al., 1996) and primates (Levine, 1993a; Heim, Owens, Plotsky, & Nemeroff, 1997). Indeed, modulation of the early-life experience of the neonatal rat by controlled experimental manipulations has been successfully used to permanently influence the HPA axis and the hormonal responses to stress during adulthood (Brunson, Avishai-Eliner, Hatalski, & Baram, 2001; Levine, 2000).

The set-point and magnitude of the responses to stress are under tight and intricate regulation (Joels & Baram, 2009; Walker & Dallman, 1993) and are influenced by both hippocampal glucocorticoid receptors (GR) and hypothalamic corticotropin releasing hormone (CRH). In both mature (Heinrichs, Menzaghi, Merlo, Britton, & Koob, 1995; Rivier & Vale, 1983) and developing (Yi & Baram, 1994) rats, CRH is released from the

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hypothalamic paraventricular nucleus (PVN) within seconds of stress onset, to influence pituitary ACTH secretion and release of adrenal glucocorticoids. These hormones interact with GRs in hippocampus, PVN, prefrontal cortex, and pituitary (Peiffer, Lapointe, & Barden, 1991; Spencer, Miller, Stein, & McEwen, 1991; Swanson & Simmons, 1989) to generate a negative feedback onto the hormonal stress response (see Fig. 1; Dallman et al., 1987).

Exposure of neonatal rats to age-appropriate physiological and psychological stressors such as cold (Yi & Baram, 1994) or prolonged or repeated maternal separation (for 3 hr or longer) results in short-term enhancement of HPA reactivity (Avishai-Eliner, Yi, Newth, & Baram, 1995; Dent, Smith, & Levine, 2000; Dent, Okimoto, Smith, & Levine, 2000; Plotsky & Meaney, 1993; Suchecki, Mozaffarian, Gross, Rosenfeld, & Levine, 1993). Interest in the *long-term* effects of early-life experience on the HPA system was driven by Levine's pioneering observation that simply separating mother and pups daily for as little as 3 min during the first weeks of life may influence neuroendocrine and behavioral responses to stress long-term, with major consequences for cognitive and emotional health throughout life (Levine, 1957; Levine & Lewis, 1959; Levine, 1993a,b; Levine, 2000). This procedure, named handling, has been applied in countless studies since: The typical handling procedure involves brief (15 min) daily separation of rat pups from their mother followed by returning the pups to the home cage. This commences on postnatal day 2 for a minimum of 1 week (Avishai-Eliner, Eghbal-Ahmadi, Tabachnik, Brunson, & Baram, 2001; Fenoglio, Chen, & Baram, 2006; Weaver et al., 2001), or up to 3 weeks (Bhatnagar & Meaney, 1995; Hess, 1969; Levine & Lewis, 1959; Plotsky & Meaney, 1993).

Handling has consistently been found to modulate the reactivity of the HPA system (Fig. 1). More specifically, concentrations of plasma corticosterone are lower in adult rats handled early in life compared to non-handled (NH) controls following exposure to novel stimuli (Levine, Haltmeyer, Karas, & Denenberg, 1967) or to subsequent handling (Ader, Stanford, Friedman, Grota, & Schaefer, 1968). In contrast, elevations in plasma corticosterone following electric shock are more rapid and initially higher in animals handled in infancy (Levine, 1962). However, in handled rats there is a more rapid return to basal levels after noxious stimulation (Haltemeyer, Denenberg, & Zarrow, 1967). Thus, rats handled in infancy seem to be endowed with improved differential response to varying intensities of stressful stimuli (but see Ader, 1970; Ader et al., 1968). They perceive and respond to mild challenging stimuli that are associated with improved cognitive function, yet recover more rapidly from strong stressors that might have adverse effects on neuronal function (Chen et al., 2010). In addition, handling leads to resilience to depressive-like behavior (Meaney et al., 1991) and improved hippocampus-dependent cognitive function (Fenoglio et al., 2005; Korosi & Baram, 2009; Liu, Diorio, Day, Francis, & Meaney, 2000) during adulthood.

More recently, the molecular basis for the altered reactivity of the HPA axis has been under study. For example, there is reduction of hypothalamic CRH in the hypothalamic PVN (Fig. 2) of handled rats, and this reduced expression is persistent (Fig. 2), and accompanied by augmented levels of hippocampal GR expression (e.g., Plotsky et al., 1993; Sanchez, Ladd, & Plotsky, 2001; Fenoglio et al., 2006). Together, these molecular changes are expected to reduce CRH, ACTH and hence corticoid release in response to stress, and augment a negative feedback that shuts-down the hormonal stress response. As mentioned above, the importance of these experimental manipulations and the related molecular changes derive from the fact that early-life experience (in combination with genetic factors) may similarly modulate the HPA axis in humans, influencing cognitive and emotional health (Nelson et al., 2007; Nemeroff & Vale, 2005; Wilson, 2007). For example, major depression is characterized by enhanced activation of the HPA axis, evident from increased cerebrospinal fluid and plasma levels of CRH and cortisol, respectively (Nemeroff, 1988). Further, it is

generally believed that resilience to depression involves the ability of the HPA system to respond differently to stresses of different magnitudes and to be shut-off effectively (Bale & Vale, 2003). Because handling produces precisely these consequences in a controlled experimental model, this model enables mechanistic studies with potential therapeutic and social implications (Bredy, Humpartzoomian, Cain, & Meaney, 2003; Fenoglio et al., 2005; Korosi et al., 2010; Nelson et al., 2007). Put differently, understanding the neuro-biological basis of the enduring consequences of this programming is fundamental for promoting healthy human neurological function and preventing stress-related cognitive and affective disorders (Nestler et al., 2002). These mechanisms form the focus of this review.

MOTHER–PUP INTERACTION IS A KEY REGULATOR OF THE PROGRAMMING OF THE HPA AXIS

The mechanisms underlying the effects of early-life handling as first proposed by Levine, Chevalier, and Korchin (1956) were thought to result, at least in part, from the direct physical effects of the procedure, for example, cooling of the pups and/or stress imposed on the pups while separated. However, others proposed that handling might act indirectly on the pups via its effects on the nature of mother–infant interaction (Barnett & Burn, 1967; Denenberg, Taylor, & Zarrow, 1969; Bell, Nitschke, Bell, & Zachman, 1974; Smotherman, Brown, & Levine, 1977). Indeed, handling has been shown to enhance mother–pup interaction by provoking bursts of maternal sensory stimulation of pups immediately after their return to the home cage (Brown, Smotherman, & Levine, 1977; Fenoglio et al., 2006; Korosi et al., 2010; and see Fig. 3). In this manner, handling likely mimics conditions that occur in nature, where short separations of the dam from the pups are common, and are associated with bouts of maternal care upon the return of the dam to the nest. In nature, it is likely that some mothers provide more care/stimulation to pups than others. This hypothesis was systematically tested in the late 1990s (Caldji et al., 1998; Francis, Diorio, Liu, & Meaney, 1999; Liu et al., 1997). Individual differences in quantity and quality of active maternal care (licking and nursing) of rats were found to be associated with differences in stress responses of the pups when they became adults. The hormonal stress response of adults reared by dams exhibiting high levels of licking and arched back nursing was reduced. This was accompanied by reduced CRH expression in the hypothalamus and increased hippocampal GR expression when compared with pups from mothers with lower levels of caring activities (Meaney, 2001; Plotsky & Meaney, 1993). In addition, the importance of sensory stimulation as a regulator of expression levels of molecules involved in the stress response such as CRH and CRH receptors has also been demonstrated (Eghbal-Ahmadi, Avishai-Eliner, Hatalski, & Baram, 1999; Fenoglio et al., 2006). Together, these studies indicate that, by recapitulating the natural variation of maternal care and creating groups that segregate more clearly (handling vs. controls), the handling procedure programs the molecules and processes that comprise the stress response.

There has been some debate in the literature about the appropriate control group when studying the effects of early-life experiences, including handling on expression of stress-related molecules such as GR and CRH, as well as on the functional outcome. One of the most widely used reference groups is one left completely undisturbed (NH). NH and handled conditions differ in several aspects (e.g., cage opening, picking up of the dam and pups and their transfer to new cages, placing them back). Because the majority of the neuroscience and behavioral literature that employs rodents is derived from studies on animal facility reared rats, the possibility has been raised that pups raised under routine animal facility care (AFR) should be the correct controls (Plotsky et al., 2005). AFR consists of exposing rats to cage changes (typically twice a week): Dams and pups undergo repeated cage cleaning involving transferring of the mother and pups to a clean, novel cage, and this procedure may therefore be considered a variant of the handling procedure. Indeed,

hypothalamic CRH levels of adults exposed to either handling or AFR rearing conditions are comparable (Plotsky et al., 1993; Viau, Sharma, Plotsky, & Meaney, 1993) and both AFR and the handling protocol produce similar neurobehavioral outcomes (Caldji, Diorio, & Meaney, 2000; Pryce, Bettschen, & Feldon, 2001; Pryce & Feldon, 2003). These data suggest that even relatively limited handling might suffice to program the HPA axis. Indeed, whereas a single handling episode does not alter hypothalamic CRH levels (Fenoglio et al., 2006), as few as five daily procedures suffice (Fenoglio et al., 2005). Therefore, we believe that a suitable control group for the handling procedure is the NH rearing condition. In the undisturbed group—in contrast to the handled group—dams are never stimulated to provide bursts of sensory stimulation to the pups by brief experimentally induced separations that take place during cage changes.

HANDLING EVOKED CHANGES ARISE SEQUENTIALLY

An important step in our understanding of the molecular and behavioral phenotype induced by the handling procedure is defining *how* it arises and the sequential steps that are involved. Persistently altered expression levels of CRH in hypothalamic neurons and of GR in the hippocampus have been established as key elements of the experience-dependent programming (Plotsky & Meaney, 1993; Fig. 1). Specifically, CRH mRNA levels in the hypothalamus are reduced, whereas GR expression levels in the hippocampus are elevated. Discovering which of these fundamental changes occurs first should help in identifying the location and nature of the initial programming steps triggered by the early-life experience. What is then the precise timing and sequence of the handling-induced alterations? Increased GR expression has been proposed as an early and critical effect of the enriched sensory input (Meaney et al., 1996; Liu et al., 1997; Francis & Meaney, 1999). The increased GR levels would then transmit negative glucocorticoid feedback more efficiently to the HPA axis, downregulating hypothalamic CRH and responses to subsequent stress. However programming of *Crh* gene expression in PVN neurons to lower levels takes place already by the end of the daily week-long handling period [postnatal day (P) 9; Avishai-Eliner et al., 2001; Fenoglio et al., 2005). This reduction is followed sequentially by attenuated hormonal responses to stress and then by enhancement of hippocampal GR expression, which take place by P23 and between P23 and P45, respectively (Fig. 1). Further support for the importance of the early reduction of CRH expression in the programming that culminates in the “handled phenotype” is apparent from the fact that reducing the activation of the CRH receptor type 1 by its endogenous ligand via a week-long administration of a selective blocker in NH rats during P10–P17, was sufficient to upregulate hippocampal GR persistently and to confer the behavioral phenotype of improved cognitive functions seen in adult handled rats in both Morris Water Maze and object-recognition tests (Fenoglio et al., 2005; Korosi & Baram, 2009). These findings establish that the modulation of CRH expression precedes the increased GR expression, indicating that programming of the levels of CRH gene expression is an early and essential step in the molecular cascade bridging maternal care and the enduring changes of the HPA system. The precise mechanism for the sequence and the timing of the onset of the reduced hormonal stress–response and augmented GR expression alterations has not yet been fully understood and requires further study.

HOW IS THE SENSORY INPUT FROM THE MOTHER CONVEYED TO CRH-EXPRESSING CELLS WITHIN PUPS’ PVN?

If the initial consequence of the augmented maternal-derived sensory input (handling) experience is to change CRH expression levels in the PVN, then we need to understand how maternal signals reach this brain region, and more specifically, the parvocellular CRH-expressing neurons in the PVN. Using the immediate-early gene Fos to visualize neurons

activated by maternal-derived sensory signals, a pathway regulating the hypothalamic PVN emerged. After a single day of handling Fos expression was induced in the bed nucleus of the stria terminalis (BnST) and the central nucleus of the amygdala (ACe; Fenoglio et al., 2006) and both these regions generally augment CRH expression in PVN (Akana & Dallman, 1997; Choi et al., 2007, 2008; Feldman, Conforti, Itzik, & Weidenfeld, 1994). In contrast, recurrent handling induced Fos expression also in the thalamic paraventricular nucleus (PVT), a region with major inhibitory output onto ACe (Bhatnagar & Dallman, 1998; Spencer, Fox, & Day, 2004). The activation of PVT neurons after recurrent handling likely altered their activity (firing rate, neurotransmitter release), changing activity of BnSTand ACe, and thus the sum and pattern of afferent information arriving at CRH-expressing neurons in PVN. Indeed, PVT has been proposed previously as a region involved in processing memories/experiences related to the stress–response system (Bhatnagar & Dallman, 1998; Bell, Bhatnagar, Akana, Choi, & Dallman, 2000).

In summary, recurrent daily handling was required for both the involvement of PVT and for reduced hypothalamic CRH expression (Fenoglio et al., 2006), suggesting that a repeated, consistent pattern of maternal care is the signal that programs CRH expression at lower levels (Fenoglio et al., 2006; Korosi & Baram, 2008).

Comprehensive characterization of the anatomic and chemical identities of the neuronal pathways conducting these signals to the hypothalamus requires further work. However, the data presented above brings to focus crucial new questions about the fundamental mechanisms of the experience-dependent programming induced by maternal sensory input. These important questions include the nature of the modified neuronal-signaling received by the CRH neuron in the PVN and the nature of the mechanisms that translate this information into persistent repression of *Crh* gene expression.

WHAT HAPPENS IN THE HYPOTHALAMIC CRH-NEURON ONCE THE SIGNAL IS RECEIVED?

Because bursts of maternal sensory stimulation (in nature or evoked by handling) elicit a signal that reaches the CRH neuron in the PVN, it is reasonable to ask what the cellular consequences of the signal are, and how they reduce CRH levels in a persistent manner. Altered activation of transcription factors involved in the regulation of CRH expression is an attractive possibility. Phosphorylation of cAMP response element-binding protein (CREB) and extracellular signal-regulated kinase (ERK) influence the initial activation of the critical cAMP-response element (CRE) domain on the *Crh* gene promoter (Seasholtz, Thompson, & Douglass, 1988). In addition, phosphorylation of the transcription factor ERK (pERK) is crucial for maintaining CREB phosphorylated beyond the first seconds after synaptic activation, contributing to plasticity at a longer timescale (West, Griffith, & Greenberg, 2002). CREB and ERK are ubiquitously phosphorylated in the PVN of undisturbed P9 rats and can therefore be candidates for deactivation by reduction of excitatory input onto these neurons (or by augmented inhibitory inputs). Indeed, recent work has demonstrated a drastic reduction in the number and function of excitatory synapses on CRH expressing neurons of handled pups (Korosi et al., 2010). These findings demonstrate a novel structural basis for the remarkable plasticity of the HPA system in response to early-life experience. In essence, these data finally answer Seymour Levine's lifelong query of *how* early-life experience might alter the brain.

The reduced excitatory input to CRH neurons in hypothalami of handled pups was translated into a strong decrease in the number of pERK immunoreactive cells in the PVN (Fenoglio et al., 2006). Accordingly, transcription of the *Crh* gene (measured by CRH mRNA) in response to separation stress decreased in the PVN of recurrently handled pups (Fenoglio et

al., 2006). This reduced transcription of the *Crh* gene should result in reduced steady-state CRH mRNA levels, as is indeed found in handled rats throughout their lives.

SUMMARY

Much progress has already been made in delineating the nature of experience-induced programming of the molecular and behavioral responses to stress, that is, the question raised by Seymour Levine over 50 years ago. The neuronal populations in which initial plasticity takes place appear to reside in the hypothalamus and the cellular changes seem to include repression of the *Crh* gene early and persistently. However, much remains unclear about the mechanisms by which experience-dependent programming takes place and future studies will examine both the initiation and maintenance of this programmed gene expression. Whereas the reduced excitatory input to CRH neurons probably initiates this programming (Korosi et al., 2010), epigenetic processes may lead to the maintenance of the molecular changes including reduction of CRH expression. These may include DNA methylation and/or neuronal restrictive silencing factor-driven histone deacetylation (Korosi et al., 2010; Meaney & Szyf, 2005; Thatcher & LaSalle, 2006).

Such future studies are necessary because this phenomenon, described originally by Seymour Levine and his peers, is of major clinical significance. Indeed, employing the principles learned from the salubrious consequences of augmented maternal care would greatly improve human health. One potential candidate for promoting resilience to affective disorders that emerges from the work described above is the CRH receptor antagonist. As mentioned above partially blocking the CRH receptor type 1 (and thus presumably reducing the consequences of activation of this receptor by CRH) in immature rats that did not receive augmented maternal care was sufficient to upregulate hippocampal GR persistently and to confer the behavioral phenotype induced by augmented maternal care (Fenoglio et al., 2005). In line with the concept of CRH receptor as a molecular target for influencing emotional and cognitive function by early-life experience, the presence of specific combinations of single nucleotide polymorphisms in the *Crhr1* gene is protective against depressive symptoms in individuals maltreated in childhood (Bradley et al., 2008; Tyrka et al., 2009). Therefore, in addition to obvious social and behavioral intervention, pharmacological interventions targeting CRH-CRH receptor signaling may enable enhanced resilience to human stress-related disorders associated with early-life experience.

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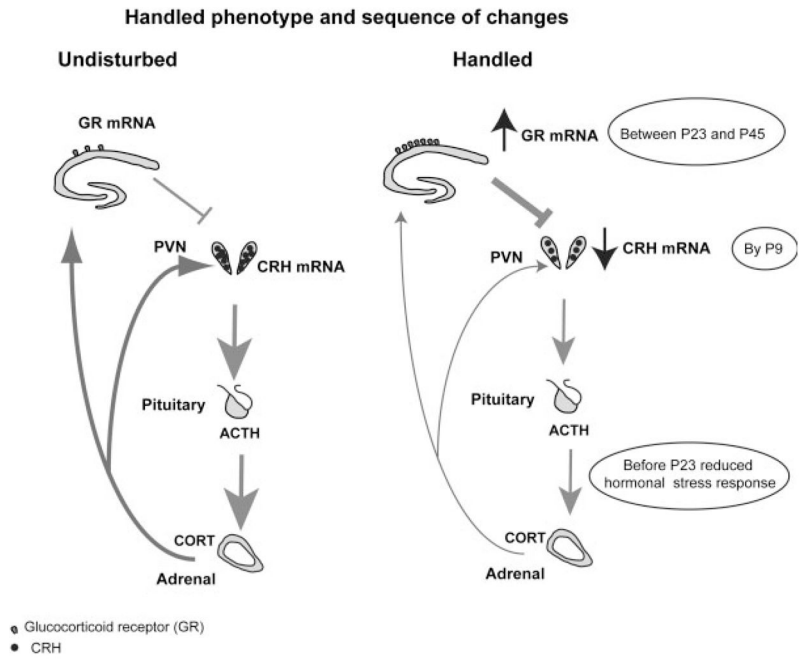

FIGURE 1.

The spectrum and sequence of molecular and hormonal changes induced by maternal care alterations via early-life handling. Corticotropin releasing hormone (CRH) expression in the hypothalamic paraventricular nucleus (PVN) of adult rats handled on postnatal (P) days P2–P9 is reduced, as are plasma ACTH and corticosterone (CORT) responses to stressors. Glucocorticoid receptor (GR) expression in the hippocampus is increased in these rats compared with controls. These changes occur in a sequential manner with reduced CRH present already by P9, followed by reduced ACTH response to stress by P23 and reduced hippocampal GR appearing between P23 and P45. The sequence of changes supports the concept of CRH modulation as an early and essential step in bridging handling-induced enhanced maternal care and the enduring changes in the HPA system.

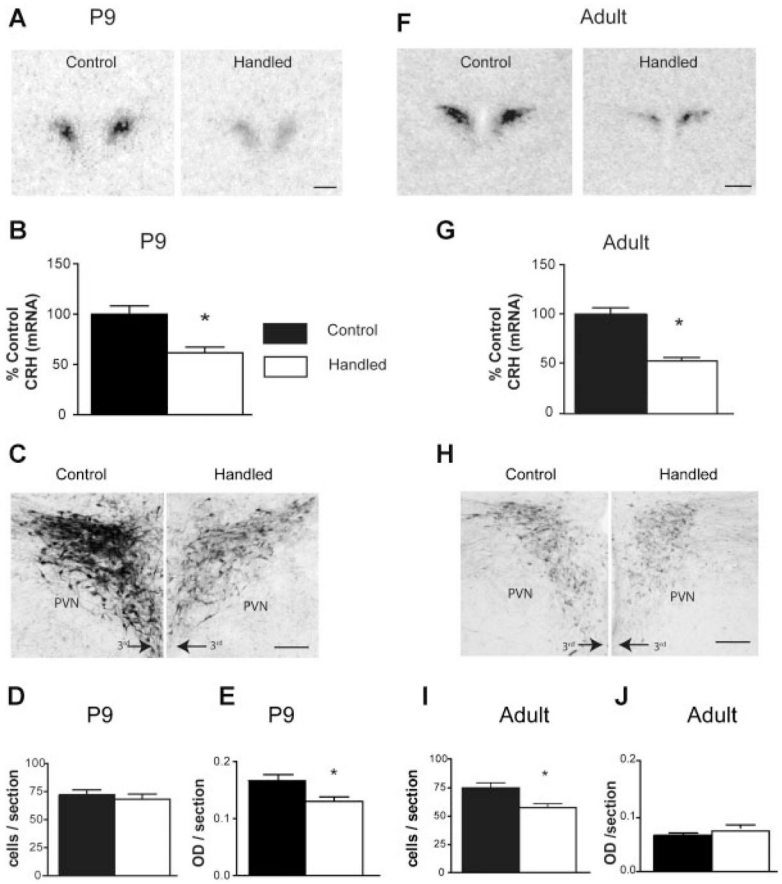

FIGURE 2.

Augmented early-life experience leads to early-onset and persistent reduction of CRH expression in parvocellular PVN at both mRNA and protein levels. (A) Representative bright-field photomicrographs of coronal sections at the level of the PVN from undisturbed controls and handled rats. The sections were subject to in situ hybridization for CRH mRNA. (B) Quantitative analysis of CRH mRNA expression in the two groups: CRH mRNA expression was reduced by 52% in postnatal day (P) 9, handled rats compared with undisturbed controls. (C) Bright-field photomicrographs, taken under similar viewing parameters, showing CRH immunohistochemistry in PVN of control and handled rats. (D) Quantitative analysis of the numbers of CRH immunoreactive (ir) neurons and (E) intensity of the immunoreactivity. The changes observed for mRNA expression were translated to protein levels as apparent from the ~20% reduction in the intensity of CRH expression in handled rats. (F,G) Representative autoradiographs after CRH mRNA in situ hybridization, and quantification of CRH mRNA signal in adult control and handled rat PVN. CRH expression in handled adult rats was 50% lower compared to controls, indicating that repressed CRH expression, found on P9, was long-lasting. (H,I,J) Bright-field photomicrographs and quantitative analysis of CRH immunohistochemistry in adult PVN. The enduring suppression of CRH expression observed at the mRNA level was translated to the protein level as evident from the ~21% reduction of CRH-ir cells in the handled rats. 3rd = third ventricle. Scale bars in A,F: 500 μm, in C,H: 200 μm. *p <.05. (Figure modified from Korosi et al., 2010.)

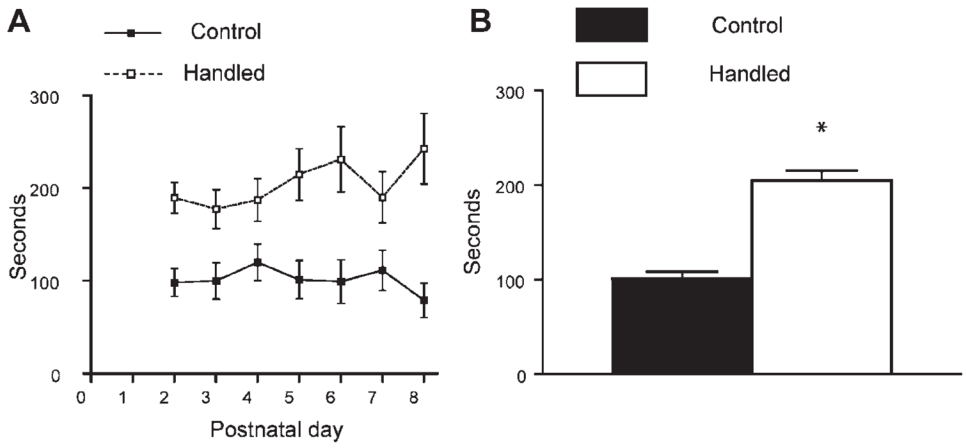

FIGURE 3.

Sensory stimulation of pups by the dam is enhanced daily after brief separation of pups from their mother. (A) Maternal stimulation of the pups, and specifically licking was observed and quantified daily from P2 to P8 during the 30 min following the return of separated pups and dams to home cages (handling procedure starting at 08:30 AM; light on at 07:00 AM.). Duration of the sensory stimulation of the pups was significantly higher in litters that were briefly separated (handled) compared to control litters on each day (n = 16 dams per group; repeated measure ANOVA $F_{1,31} = 39.94$, $p < .0001$). (B) Collapsed for the whole week, duration of nurturing activity of the dams was twofold higher in handled litters compared with controls. *p <.0001.