

Parental Deprivation Induces N-Methyl-D-Aspartate-Receptor Upregulation in Limbic Brain Areas of *Octodon degus*: Protective Role of the Maternal Call

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SUMMARY

An optimal coordination between parents and their offspring involves a sequence of reciprocal behaviors to ensure the adequate care of the young, which is critical for a healthy physical, emotional, and social development. Parental deprivation, particularly an impaired child-mother attachment, induces lasting changes in emotional as well as in cognitive capacities in later life. We assessed in the South American precocial species, *Octodon degus*, whether alterations of glutamatergic function of the limbic system induced by parental deprivation may be a neural correlate for such behavioral changes. Further, we analyzed whether the mother's voice can protect from separation-induced changes of brain function. Changes of N-methyl-D-aspartate (NMDA) receptor expression were examined in the following three groups of 2-week-old *Octodon degus* pups: (I) control animals who remained undisturbed with the family; (II) animals who were repeatedly separated from the family and individually placed in an unfamiliar environment for behavioral analysis (open field); and (III) animals who were treated like the group

described under (II) but were presented with maternal vocalizations during separation. Relative to those in the control group I, the animals in group II showed an upregulation of NMDA receptor density in the (a) anterior cingulate, prelimbic, infralimbic, and anterior insular cortices; (b) CA1/stratum radiatum; (c) CA1/stratum lacunosum moleculare and CA3/stratum radiatum; and (d) in the basomedial amygdaloid nucleus. Presentation of the maternal call during the separation period (group III) suppressed the separation-induced NMDA receptor upregulation in all regions. The results demonstrate that early life events can influence the expression of transmitter receptors and that maternal behavior, acting to control the pup's socio-emotional environment, is a key factor for regulating such developmental events.

INTRODUCTION

In sensory system development, genetically preprogrammed neuronal plasticity is highly sensitive to environmental stimulation. This experience-regulated plasticity, on the one hand, is

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beneficial for an adaptive and appropriate functional development of brain pathways. On the other hand, such plasticity can be detrimental because of the brain's high vulnerability toward early adverse environmental conditions, which can lead to the abnormal development of both brain and behavior. Quite analogous to the impaired functional maturation of the sensory systems after sensory deprivation, either early socio-emotional deprivation or adverse, stressful emotional experiences may induce an impaired or altered development of the limbic pathways. Such functional deficits in the limbic system may be the neural correlate of behavioral disturbances and cognitive and emotional deficits, which are typically observed in socially deprived animals and humans (Hall, 1998; Suomi, 1991; Spitz, 1945; Gray, 1958; Skeels, 1966). The neural mechanisms underlying such early developmental disturbances, however, are not well understood.

For the newborn individual, one of the most stressful and fear-inducing experiences is separation from the parents and exposure to an unfamiliar environment. This experimentally easily inducible and well-controlled paradigm provides an ideal model for the investigation of deprivation- and experience-regulated brain development. Studies in this animal model revealed a variety of changes in the composition of different transmitter systems, including the monoaminergic and nitric oxide systems (Braun et al., 2000; Poeggel et al., 1999; 2000; Thoa et al., 1976; Weinstock et al., 1978; Jones et al., 1992), but only a few studies analyzing changes on the receptor level have been performed (Liu et al., 2000). As glutamate is the most dominant excitatory transmitter in the brain and because its NMDA receptor subtype is not only involved in learning but also plays a role during brain development, we investigated whether repeated brief separation from the parents during the first weeks of life—namely, a period during which the pups are still highly dependent

on parental care—changes the density of NMDA receptors in limbic brain regions. NMDA receptors are involved in the brain's response to environmental cues (Lil-Jequist et al., 1993) and are activated by stressful events (Shors & Mathew, 1998), including the expression of anxiety that is induced by maternal separation (Kehne et al., 1991). NMDA receptors participate in processes of juvenile and adult learning (Hattori et al., 1990; Flood & Morley, 1998; Bock et al., 1996, 1997; Rouillet et al., 1999), brain maturation (Hattori & Wasterlain, 1990), neuronal plasticity (Staubli, 1995; Bock & Braun, 1999), and formation of spatial memory (Izquierdo & Medina, 1997; Guitierrez et al., 1999). They also play a role in the pathogenesis of a variety of diseases, including epilepsy (Musshoff et al., 2000; Folbergrova et al., 2000; Mikuni et al., 1999), Parkinson's disease (Blandini et al., 1996), and schizophrenia (Olney et al., 1999; Olney & Farber, 1995).

A further aim of this study was to investigate the regulatory role of maternal behavior—in particular vocal communication with her offspring—on deprivation-induced receptor changes. For studying the role of maternal vocalizations on the pup's motivational and emotional status at the behavioral level and in relation to early postnatal brain development, the *Octodon degus*—a South American precocial species formerly classified as a caviomorph rodent but now considered to belong to *lagomorpha* (rabbits)—offers certain unique advantages. Most remarkable is that both parents engage equally in the care of their offspring (Wilson, 1982). Unlike rats and mice, degu pups are born with functional sensory systems, and this relative maturity of the sensory systems allows the newborn pups, like human newborns, to perceive and to respond to familiar and novel stimuli, including con-specific vocalizations, immediately after birth. The species is characterized by a highly elaborated vocal repertoire, which is used for communication among parents, offspring, and other

group members (Fulk, 1976). The newborn pups must learn to recognize and to respond to the mother's vocalizations within the first days of life (Poeggel & Braun, 1996; Braun & Scheich, 1997), which is analogous to behavior observed in human babies (De Casper & Fifer, 1980).

EXPERIMENTAL PROCEDURES

All experiments were performed in accordance with the European Communities Council Directive of November 1986 (86/609/EEC), and all efforts were made to minimize both the suffering and the number of animals used in the present study.

The degus used in this study were bred in our colony. Family groups consisting of an adult couple and their offspring were housed in standard rat cages (length \times height \times depth: 53 \times 24 \times 32 cm). The animals were exposed to an artificial light/dark cycle with 12 h lights on. Fresh drinking water and rat diet pellets, vegetables, and fruit were available *ad libitum*. The animal rooms were air conditioned, with an average temperature of 22 °C.

Behavioral experiments

The behavioral experiments were intended to give a rough estimate of the pup's behavior during the separation period and to test if maternal vocalizations have any effect on their behavior. The pups remained undisturbed with their families until postnatal day 7 (P7; day of birth = P0). On P8, an analysis of exploratory activities during parental separation in an unfamiliar environment (size of the open field: 70 \times 70 \times 24.5 cm) was started in the following two experimental animal groups:

- *Short parental separation (SPS)*: Animals (14 males, 17 females) were individually placed into the open field arena. This procedure, which induces a brief separation from parents

and siblings and exposure to a novel environment, was performed twice daily for 3 min each session, starting at P8 and continuing through P10, resulting in a total of 6 parental separation sessions and a total parental separation time of 18 min.

- *Short parental separation + tone (SPS+T)*: Animals (18 males, 13 females) were treated like those in the SPS group, but a maternal call (= tone) was presented during the 3 min of parental separation in the open field. For details of the acoustic features of the maternal call, see (Poeggel & Braun, 1996; Braun & Scheich, 1997).
- *Normal (NORM)*: Age-matched animals (5 males, 8 females), who had been raised under socially undisturbed conditions with their families, served as a control group for the receptor autoradiography experiments (Fig. 1). Locomotor activity was analyzed as running activity in cm/3 min separation. The age for the deprivation procedure and the time of brain analysis were chosen from previous studies showing that by P8, degus pups have developed a clear behavioral response toward the maternal call (Poeggel & Braun, 1996; Braun & Scheich, 1997).

Ligand autoradiography

For the autoradiographic analysis, 14-day-old animals from the SPS (5 males, 6 females) and SPS+T (6 males, 6 females) groups were used. On P14, the animals of groups NORM, SPS, and SPS+T were decapitated, and the brains were removed from the skull and frozen at -80° C. Series of 10 μ m thick sections were cut on a cryostat (Micron, Dortmund, Germany), mounted on gelatin-coated slides, and stored at -20° C until use.

The method for incubation was performed as described in Schnabel and Braun (1996). In the present study, we applied a saturable ligand

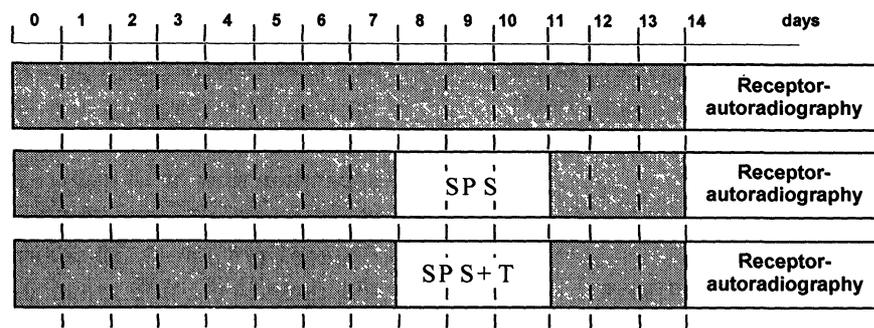


Fig. 1: Experimental procedure for brief parental deprivation and exposure to a novel environment (Open field) with (SPS+T = short parental separation + tone) and without (SPS = short parental separation) presentation of maternal vocalization.

concentration to analyze maximal binding to the receptor. The sections of all three animal groups were processed simultaneously.

After preincubating for 30 min in the incubation buffer, the sections were incubated for another 2 h with 20 nM [^3H]-MK801 (NEN, Köln, Germany) (30 Ci/mmol) in 50mM Tris-HCl at room temperature. Nonspecific binding was determined by a parallel incubation in the presence of 100 nM MK801. Incubation was terminated by rinsing the sections three times for 10 min each in ice-cold buffer, after which they were briefly dipped in cold distilled water and dried in a stream of cold air. For quantitative analysis, slides of all three groups, together with tritium standards (Biotrend, Köln, Germany), were exposed for 6 d to imaging plates (Fuji, Japan). The resulting radiation images on the imaging plates were read by the scanner unit of the imaging system BAS3000 (Fuji). The photostimulated luminescence (PSL) was measured in each measuring field (integrated PSL over the area) of the brain and in the tritium standards, the background was subtracted, and the resulting PSL was calculated per mm^2 using TINA2.9 software (Raytest, Straubenhardt, Germany).

For each animal and each brain region, six sections over a rostro-caudal extension of 250 μm

were measured; after subtracting the background intensity, we calculated the mean labeling densities for each brain region. Brain regions were selected for quantitative analysis according to their distinct labeling and clear identification from adjacent areas.

The following brain regions were analyzed (Fig. 2):

1. *PFC subregions*:
 - a) anterior cingulate cortex
 - b) precentral medial cortex
 - c) pre- and infra-limbic cortex
 - d) anterior insular cortex.
2. *Hippocampus*:
 - e) CA1/stratum radiatum
 - f) CA1/stratum lacunosum moleculare
 - g) CA3/stratum radiatum.
3. *Amygdala*:
 - h) basomedial amygdaloid nucleus.

To test for gender specific variations and for hemispheric asymmetries, we carried out separately all quantitative analyses for male and female pups and for right and left hemispheres, respectively.

Receptor densities were calculated as molar quantities of the bound radioligand per unit protein (fmol/mg) by calibrating the measured PSL/ mm^2 against tritium standards (Biotrend, Köln, Germany)

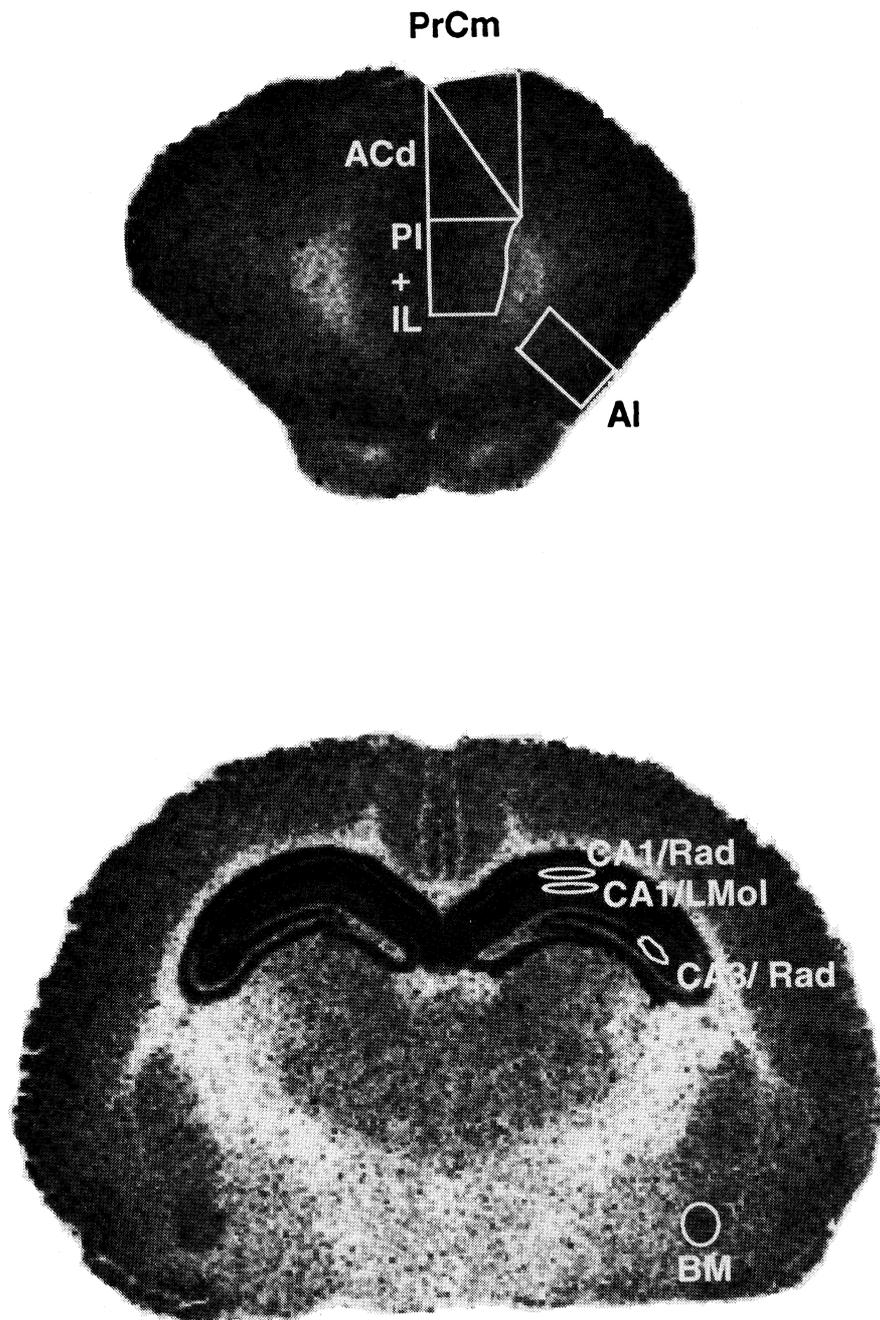


Fig. 2: Topographic localization of NMDA receptors in the forebrain of 2-wk-old *Octodon degus* demonstrated by binding to the antagonist [3 H]-MK801. Frontal sections of anterior (top) and more posterior (bottom) levels of the forebrain. In the outlined areas, receptor densities were quantified using densitometric image analysis. PrCm, precentral medial cortex; ACd, anterior cingulate cortex; PL+IL, pre- and infra-limbic cortex; AI, anterior insular cortex; CA1/Rad, stratum radiatum of CA1; CA1/LMol, stratum lacunosum moleculare of CA1; CA3/Rad, stratum radiatum of CA3; BM, basomedial amygdaloid nucleus.

TABLE 1

Locomotor activity during short-term parental deprivation in the open field with and without presentation of parental vocalizations in the first experimental day (1+2 trials)

Distance run (cm)		p value
SPS [†]	SPS+T	
495.94 ± 22.67	374.24 ± 33.47	0.005

[†]number of animals = 31; SPS = short parental separation; SMS+T = short parental separation and parental vocalization; n = number of animals. Values are mean ± standard error in fmol/mg. The significance of differences between means was determined with Mann-Whitney U-test; p values are for the SPS group compared with the SPS+T group.

as nCi/mg, which were then converted into fmol/mg. The behavioral data and receptor-ligand binding (bound ligand per unit protein) were first analyzed by the Kruskal-Wallis ANOVA, when $p \leq 0.05$ a pairwise comparison was made using the two-tailed Mann-Whitney U-test.

RESULTS

Behavior

No difference in locomotor activity was found between male and female pups in both behavioral test paradigms, therefore the data for both genders were pooled. The presentation of parental vocalizations (SPS+T group) significantly reduced the running activity during short-term parental separation, but only during the first two periods on the first experimental day (Table 1).

Ligand autoradiography

In the medial prefrontal cortex (mPFC), the highest level of NMDA-receptor density was

detected in the upper cortical layers, as compared with the middle and deeper layers (see Fig. 2). No differences were found between the measured subregions of the mPFC with respect to their NMDA receptor density. As no gender differences and hemispheric asymmetries were observed in any investigated group, the values were pooled.

After short-term parental separation in a novel environment (SPS group), a significant increase of NMDA-receptor density was measured in the anterior cingulate, pre- and infra-limbic, and pre-central medial cortices as compared with the NORM control group. In the SMS group, the anterior insular cortex showed a similar but nonsignificant trend toward increased NMDA receptor density (Fig. 3). With regard to NMDA-receptor density, animals that were exposed to parental vocalizations during parental separation (SPS+T group) did not differ from animals of the NORM control group. Except for the anterior insular cortex, in all analyzed mPFC regions, the animals of the SPS+T group displayed significantly lower NMDA-receptor densities when compared with those of the SPS group (Fig. 3).

In all measured hippocampal regions, the animals from the SPS group showed a clear

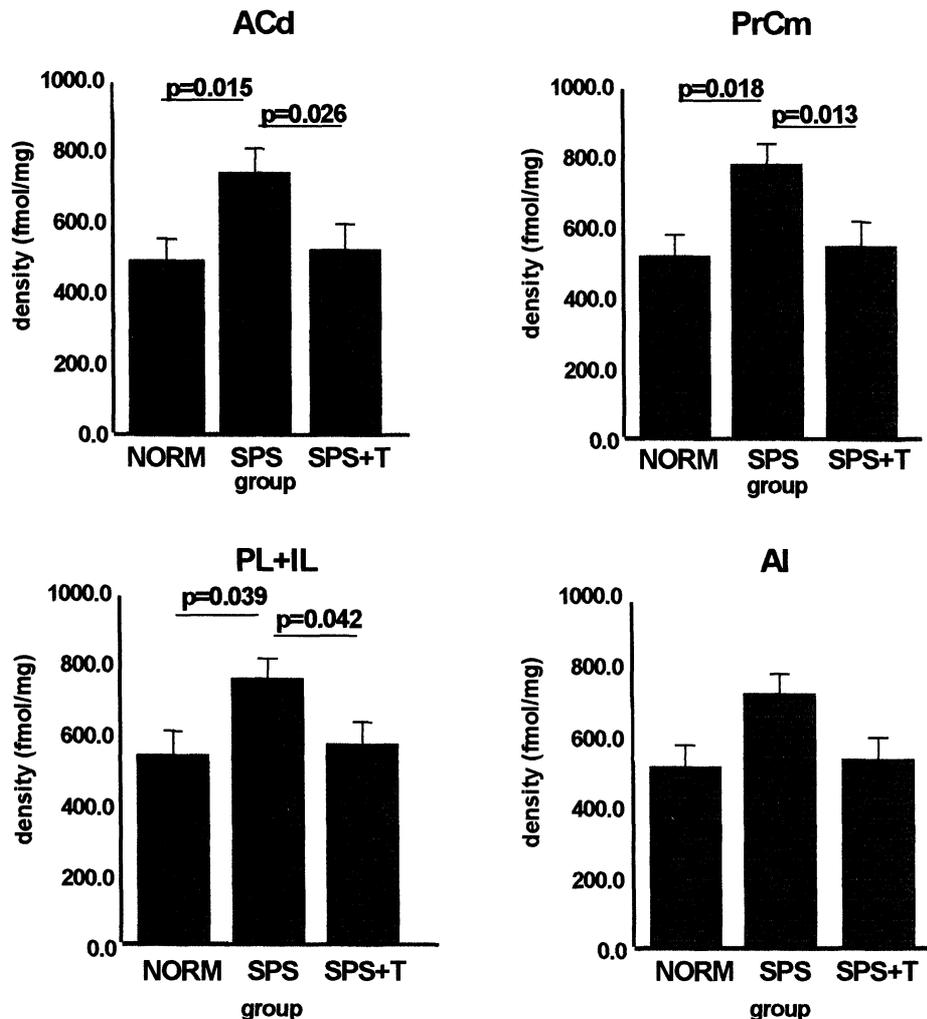


Fig. 3: Medial prefrontal cortex: Changes of NMDA-receptor density after brief parental deprivation and exposure to a novel environment (open field) with (SPS+T = short parental separation + tone) and without (SPS = short parental separation) presentation of parental vocalization. PrCM, precentral medial cortex; ACd, anterior cingulate cortex; PL+IL, pre- and infra-limbic cortex; AI, anterior insular cortex.

increase of NMDA-receptor density compared with that in the **NORM** group, which was significant for CA1/stratum lacunosum moleculare and CA3/stratum radiatum, but not for CA1/stratum radiatum (Fig. 4). Similar to that in the cortical regions, the NMDA-receptor density of the **SPS+T** group did not differ from that of the **NORM** control animals in all measured hippo-

campal regions. The presentation of the parental call (**SPS+T** group) significantly suppressed NMDA-receptor upregulation in the CA1/stratum lacunosum moleculare and the CA3/stratum radiatum hippocampal regions (Fig. 4). In the CA1/stratum radiatum, a similar suppressive effect of the parental call was observed but did not reach significant values.

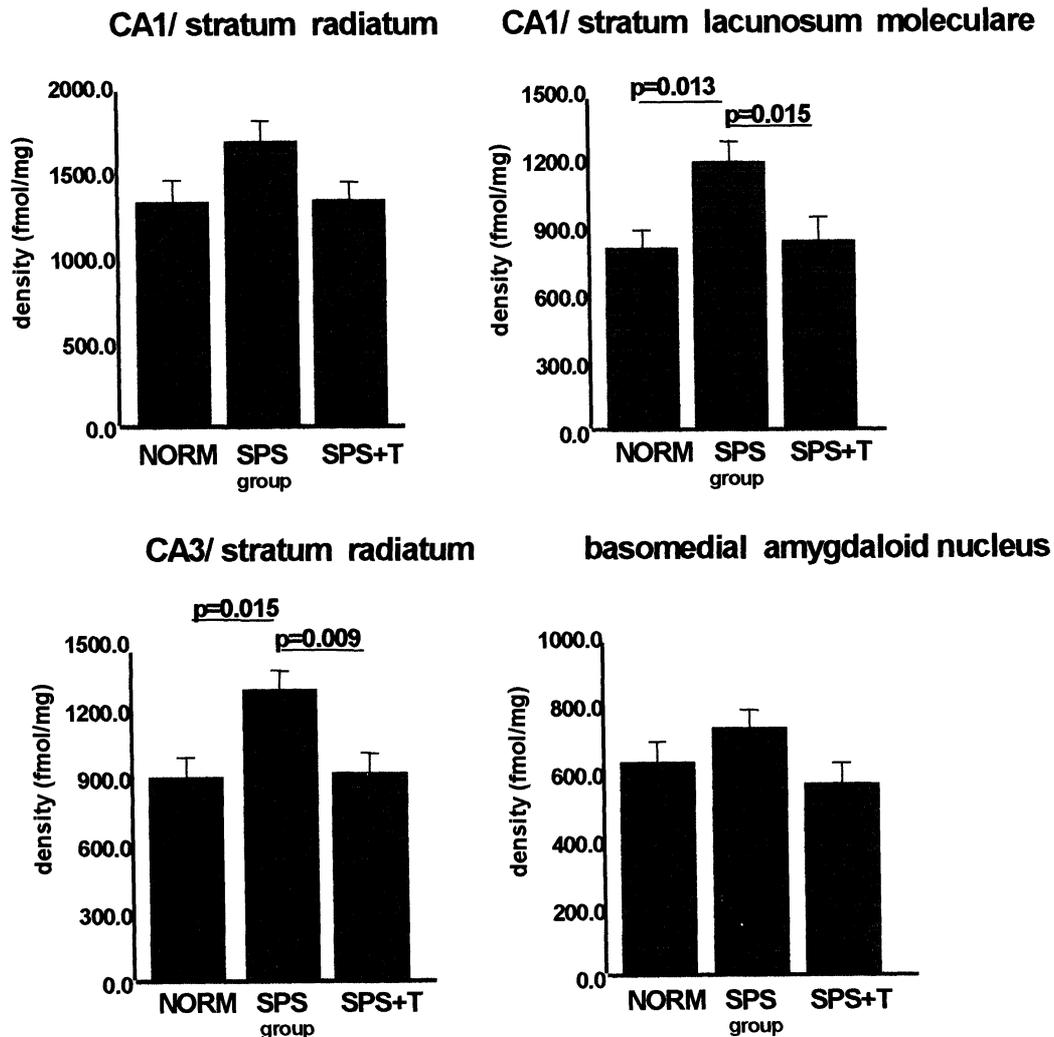


Fig. 4: Hippocampus and amygdala: Changes of NMDA-receptor density after brief parental deprivation and exposure to a novel environment (open field) with (SPS+T = short parental separation + tone) and without (SPS = short parental separation) presentation of parental vocalization. Values are mean \pm standard error.

In the basomedial amygdaloid nucleus, the differences observed among the three groups showed the same trend as those for the other brain areas, but these differences did not reach statistical significance (Fig. 4).

DISCUSSION

The results of the present study in 2-wk-old *Octodon degus* pups demonstrate that repeated,

brief changes of the socio-emotional environment can alter glutamatergic function in the juvenile brain. An increase of NMDA receptor density in limbic brain areas was observed 3 days after 6 episodes of brief parental deprivation and exposure to an unfamiliar environment. This upregulation was suppressed by the acoustic presence of the mother (parental vocalizations) during the separation period. The behavioral observations revealed a suppressive effect of parental vocalizations on exploratory activity, most likely

through its 'anxiolytic' effect, namely, by reducing the pup's fear.

A mother's voice is an intense acoustic signal that can already be measured in the amniotic environment; it has both acute and enduring effects on the development of the brain, as well as on later emotional development (Fifer & Moon, 1994). Parental vocalizations can be regarded as a powerful emotional signal, which in many species, including humans, is an essential part for the establishment and maintenance of the child-mother attachment. Parental vocal communication regulates the pup's physical development (Poeggel & Braun, 1996, Braun & Scheich, 1997) and behavior, most likely by protecting the pup from exposure to frightening situations and by reducing its level of anxiety during stressful experiences. Previous research showed that during the first postnatal week, *Octodon degus* pups learn the meaning (including its emotional context) of the 'mothering call', which is used by the dams specifically during nursing episodes (Poeggel & Braun, 1996; Braun & Scheich, 1997), and that these vocalizations evoke strong approach behavior in the young pups. On the behavioral level, this fear-reducing function of the mother's voice is further documented in the present study in the down-regulation of running activity, which occurred only during the first two episodes of parental deprivation—namely, when the pups still felt insecure in an unfamiliar situation, but not after they had habituated (trials four to six). On the brain systems level, the finding that the mere acoustic presence of the mother (the 'mothering call') is already sufficient to 'buffer' the stress/anxiety-induced NMDA receptor upregulation in the limbic system may also be related to the 'anxiolytic' effect of parental vocalizations.

Assuming the 'anxiolytic' effect of parental vocalization on behavior and brain function, the main contributing factors to the NMDA receptor upregulation appear to be stress and anxiety during

the separation period. A participation of NMDA receptor activation in emotional stress during parental separation has been shown in pharmacological behavioral experiments in pups of laboratory rats, in which the application of NMDA receptor antagonists suppressed ultrasonic vocalizations which represent a reliable indicator for fear and anxiety (Kehne et al., 1991). The few studies done in very young animals demonstrate that the juvenile brain is sensitive to stressful experiences and is capable of changing its transmitter receptors in response. In adult rodents, changes of glutamatergic receptor subtypes have been observed in a variety of stress paradigms (Akinci & Johnson, 1993; Bartanusz et al., 1995; Krugers et al., 1993). Furthermore, it has been reported that the activation of NMDA receptors participates in responses to stressful situations (Shors & Mathew, 1998; McEwen, 1999) by stimulating pituitary hormone release (Jezova et al., 1995; Zelena et al., 1999) and the synthesis and release of dopamine within the striatum, hippocampus, substantia nigra (Doherty & Gratton, 1997; Zigmond et al., 1998), ventral tegmental area, and PFC (Jedema & Moghaddam, 1994; Takahata & Moghaddam, 1998). An increase of AMPA but not of NMDA receptors has been found after 1 h of acute immobilization/shock stress (Tocco et al., 1991); after repeated immobilization stress, levels of GluR1 mRNA were elevated in the hippocampus (Schwendt & Jezova, 2000), whereas social stress induced a decrease of AMPA receptors (Krugers et al., 1993).

It is still unclear whether these environmentally induced transmitter changes are adaptive and beneficial for the animal's coping with future psychosocial challenges or whether they are detrimental and impair the animal's tolerance toward novel and stressful fear-inducing stimuli. Upregulation of NMDA receptor density occurs in limbic structures, such as the hippocampus and medial prefrontal cortex, and with a weaker

response also in the amygdala—regions that are involved in the perception of emotional signals and in the regulation of behavioral responses. In adult rodents, the activation of NMDA receptors has been shown to be responsible for stress-induced alterations of LTP and LTD and appears to mediate stress-induced neuronal atrophy in the hippocampus (McEwen & Magarinos, 1997). In our juvenile animals, most brain areas that are involved in emotional perception and behavior—such as the anterior cingulate cortex with its reciprocal connections to the amygdala, a central fear system that is involved in both the expression and acquisition of conditioned fear (LeDoux, 1998; Staubli, 1995), and the hippocampus as a structure involved in learning and memory formation—showed altered NMDA receptor densities, which could transiently or permanently alter the animals responsiveness and behavioral strategies toward changes in the social environment. These observations—together with our finding that, at least in juvenile animals, transmitter receptors can rapidly change during and after exposure to a behavioral test procedure—should be considered whenever behavioral test series are designed. One should be aware that the first behavioral trial may already alter the biochemical composition of the brain and thereby influence the animal's performance in subsequent trials.

The NMDA receptor upregulation was still measurable 4 days after the last episode of parental separation, suggesting that the receptor changes may persist during the pre- and post-weaning periods and perhaps even until adulthood, but this topic requires further investigation. More-over, it remains to be analyzed if and in which way transient or lasting abnormally high NMDA receptor densities during critical phases of postnatal maturation of brain and behavior can result in cognitive impairments and in lasting changes of emotionality, as has been reported in humans after parental deprivation, severe stress, and juvenile traumatic experiences.

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