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A diverse development of 5-HT1A receptor binding is relevant to behavioral differences observed in adult mice of two genetically closely related inbred strains

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ABSTRACT

Only few genetic loci were supposed to be crucial for strong behavioral differences, especially in locomotion and aggression, in two closely related mice inbred strains: AB/Halle (ABH) and AB/Gatersleben (ABG). Previously we reported remarkable strain differences in 5-HT1A receptor binding in adult mice. In the present study, we were interested if the strain-specific 5-HT1A receptor binding pattern is already present very early in ontogeny which could indirectly hint at a gene that is differentially regulated in these 2 mouse strains. Since the 5-HT1A receptor is involved in the regulation of locomotion and aggression, one genetic determinate for the behavioral differences in ABH and ABG mice would have been found. Therefore, we measured [^{3}H]8-OH-DPAT specific binding at postnatal day (PND) 1 and 21 (weanlings) using in vitro autoradiography. 5-HT1A receptor binding was not significantly different at PND 1 between strains. However, in weanlings the same 5-HT1A receptor binding pattern was observed as in adults, i.e. ABH mice display a higher forebrain 5-HT1A receptor binding compared to ABG mice. So the strain-specific forebrain 5-HT1A receptor binding pattern develops during the first 3 postnatal weeks and genetically driven mechanisms seem to be crucial. However, early environmental influences, e.g. differences in maternal care, can't be excluded.

1. Introduction

Behavior is the result of complex interactions between an organism's genes and environmental influences. Genetically closely related mice strains differing in behavioral traits due to separate or selective breeding are useful tools to get insights into the impact of these factors. In line with this we used for our analysis two genetically closely related mouse inbred strains derived from the original inbred strain AB (from Dr. Agnes Bluhm) that came in 1959 to Jena (Staats, 1985). Some breeding pairs from this original strain AB/Jena came in 1960 to Gatersleben and a new strain was established: AB/Gatersleben (ABG). In 1976 other breeding pairs have been transferred from Jena to Halle and were the start point of the strain: AB/Halle (ABH). Both breeding lines have been transferred to Magdeburg in 1984. The prolonged inbreeding procedure established two AB strains (ABH and ABG) that can be best described as two genetically closely related inbred strains that differ especially in aversive behavior. ABG males are docile in groups, but ABH males exhibit high spontaneous aggression against male members of a group (Schneider-Stock and Epplen, 1995). Isolation housing was applied to measure individual male aggression independent on group rank order and to foster aggression expression. High aggression levels were again found for ABH mice, whereas ABG mice did not develop isolation-induced aggression even after long isolation periods (Schiller et al., 2006; Schneider et al., 1992). Genetic analyses revealed an autosomal dominant inheritance involving few loci (Schicknick et al., 1993). Multilocus DNA fingerprint studies underlined also the importance of an aggression-linked genetic polymorphism (Schneider-Stock and Epplen, 1995). Previously we reported further differences between 12-week-old ABH and ABG mice (Schiller et al., 2006): ABH mice are more active and more explorative compared to ABG mice, but both strains did not differ in anxiety-related behavior. We have found also several strain differences in CNS neurochemistry and in 5-HT receptor binding. In detail, we observed significantly higher 5-HT1A receptor binding in cortical areas, the hippocampus, and in the cortical/medial amygdala in adult ABH compared to ABG mice (Schiller et al., 2006). Forebrain 5-HT1A receptors are involved in the regulation of locomotor activity, exploration, anxiety, and aggression (File and Gonzalez, 1996; Gross et al., 2002; Korte et al., 1996; Mignon and Wolf, 2002; Popova, 2006; van der Vegt et al., 2001). Therefore, the question arises if the strain-specific 5-HT1A receptor binding pattern is a genetically determined trait marker in AB mice which might have a functional relevance for the differences observed in locomotion, exploration, and aggression. If so, the characteristic strain-dependent 5-HT1A receptor binding pattern should be found very early in ontogenetic development and should be consistent over time. To reveal the development characteristics of 5-HT1A receptor binding we investigated [^{3}H]8-OH-DPAT binding in 1-day- and 3-week-old

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(weanlings) ABH and ABG pups. Receptor data from 12-week-old AB mice that were published previously (Schiller et al., 2006) were included for analysis.

2. Materials and methods

2.1. Animals and housing

Male ABH and ABG albino mice from our own breeding facilities were used for receptor analysis. Breeding pairs from each inbred strain (ABH and ABG respectively), kindly provided by Prof. Sachser (Institut für Neuro-und Verhaltensbiologie, Westfälische Universität Münster), were housed in standard cages (polyacryl; 37.5 cm × 22 cm × 15 cm; EHRET, Germany) with sawdust bedding (SSNIFF, Germany) under a controlled environment (21 ± 2 °C, 40–60% air humidity, 12 h/12 h light−dark cycle: light on at 6.00 a.m.) with free access to food and water. Paper towels were provided for nest building. Males were removed immediately after birth of offspring. Day of birth was set as postnatal day (PND) 0. Housing and experiments were performed in accordance with the national and international guidelines and approved by a governmental committee (75-9168-11-1.10/97, Regierungspräsidium Dresden, Germany).

2.2. In vitro autoradiography

2.2.1. Brain preparation

Six males of each strain (2 pups from 3 different litters) were decapitated at PND 1 respective PND 21 for in vitro autoradiography. Brains were rapidly removed, frozen using crushed dry ice, and stored at −80 °C until use. Frontal brain slices (20 μm) were cut with a cryostat (Leica, Bensheim, Germany), thaw-mounted onto glass slides, air-dried for 120 min, and stored at −20 °C. Slices for 5-HT1A receptor analysis were determined with an atlas of the developing rat nervous system (Paxinos et al., 1994) and a mouse brain atlas (Franklin and Paxinos, 1997). Specific binding of [^{3}H]8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin) was analyzed in the following planes at PND 1 and PND 21:

plane 1 (septum-level) parietal cortex
plane 2 (dorsal hippocampus-level) hippocampus — CA1 region, cortical and medial amygdaloid nuclei
plane 3 (raphe-level) dorsal raphe nucleus

Fig. 1 shows Nissl-stained planes and corresponding autoradiograms for 21-day-old mice.

2.2.2. Incubation

The radiolabelled 5-HT1A receptor agonist [^{3}H]8-OH-DPAT was used (Perkin Elmer, Rodgau-Jügesheim, Germany). Preliminary tests were done to reveal the appropriate [^{3}H]8-OH-DPAT concentration since several studies showed differences in K_d (dissociation constant) between the young and adult rodent brain (Daval et al., 1987). We analyzed a concentration of 0.5, 1.5, 2.0, and 3.0 nM in pups (data not shown). The best binding property and resolution were observed at 2 nM, which is the already used concentration for in vitro autoradiography in the adult rodent brain. So incubation procedure was done in the same manner as previously described in detail for 12-week-old AB mice (Schiller et al., 2006).

2.2.3. Data analysis

After incubation slides were exposed to [^{3}H]-sensitive imaging plates (Raytest, Straubenhardt, Germany) together with [^{3}H] microscale standards (Amersham Biosciences, Piscataway, USA) for 10 days. Thereafter, imaging plates were scanned by a bioimaging analyzer (Fuji, Japan) and analyzed with the software AIDA 2.11 (Raytest, Straubenhardt, Germany). Nissl-stained reference slices adjacent to the sections processed for autoradiography were used to identify brain regions. Data evaluation could not be done in several cases, i.e. the brain tissue was destroyed during incubation or the slice used for incubation did not match exactly the brain plane necessary for quantitative densitometry. So, specific binding means (fmol/mg protein) reported for each group were calculated from 4 to 6 animals.

2.3. Statistical analyses

Data of 12-week-old ABH and ABG mice from our previous publication (Schiller et al., 2006) were included for comparative analysis. All values reported are means +/−S.E.M. Statistical tests were performed using SPSS 17.0 for Windows NT (SPSS Software GmbH, München, Germany). Receptor measures were normally distributed (*Shapiro–Wilk*-test applied). A two-way ANOVA with strain (ABG vs. ABH) and age (PND 1 vs. PND 21 vs. 12 weeks) as between subject-factors was applied. A probability level of ≤ 0.05 was used to determine statistical significance. Post-hoc comparisons were done with the *Student's* t-test. The obtained results were adjusted with *Bonferroni*-correction for multiple comparisons within one brain region and p was then set as follows: $p \leq 0.016$ for strain comparisons and $p \leq 0.008$ for age comparisons.

3. Results

Results are presented in Fig. 2.

3.1. Results of the two-way ANOVA

In the parietal cortex the strain ($F(1, 25) = 37.0$, $p \leq 0.001$), the age ($F(2, 25) = 669.6$, $p \leq 0.001$), and the interaction of both ($F(2, 25) = 6.0$, $p \leq 0.01$) have significant effects on [^{3}H]8-OH-DPAT binding. The 5-HT1A receptor binding in the cortical/medial amygdaloid nucleus is significantly influenced by the strain ($F(1, 21) = 4.6$, $p \leq 0.05$) and animal's age ($F(2, 21) = 220.2$, $p \leq 0.001$), whereas the interaction of both factors failed to reach the significance level ($F(2, 21) = 2.7$, $p \leq 0.09$). In the hippocampus all factors have a significant influence: strain ($F(1, 22) = 22.24$, $p \leq 0.001$), age ($F(2, 22) = 591.1$, $p \leq 0.001$), and strain x age ($F(2, 22) = 6.51$, $p \leq 0.01$). In the raphe nucleus the factor strain has no significant effect on 5-HT1A receptor binding, but animal's age ($F(2, 21) = 119.1$, $p \leq 0.001$) and the interaction between strain and age ($F(2, 21) = 5.0$, $p \leq 0.01$) have significant effects.

3.2. Age effects on 5-HT1A receptor binding

5-HT1A receptor binding is very low one day after birth in all brain regions analyzed. [^{3}H]8-OH-DPAT specific binding values are, independent on brain region and strain, consistently higher in weanlings and adults compared to those obtained at PND 1 (all comparisons $p \leq 0.008$). Between 3 and 12 weeks of age, 5-HT1A receptor binding increased in the cortical/medial amygdaloid nuclei in both strains ($p \leq 0.008$) and in the CA1 field of the hippocampus of ABH mice ($p \leq 0.008$). But it decreased during the same period in the parietal cortex in both strains ($p \leq 0.008$) and in the dorsal raphe nucleus in ABG mice only ($p \leq 0.008$).

3.3. Strain effects on 5-HT1A receptor binding

No significant strain differences in 5-HT1A receptor binding are present at PND 1 in the hippocampus and cortical/medial amygdala. Strain differences in the parietal cortex ($p = 0.02$) and dorsal raphe nucleus ($p = 0.035$) did not reach significance at PND 1 after *Bonferroni*-correction. Higher 5-HT1A receptor binding is observed

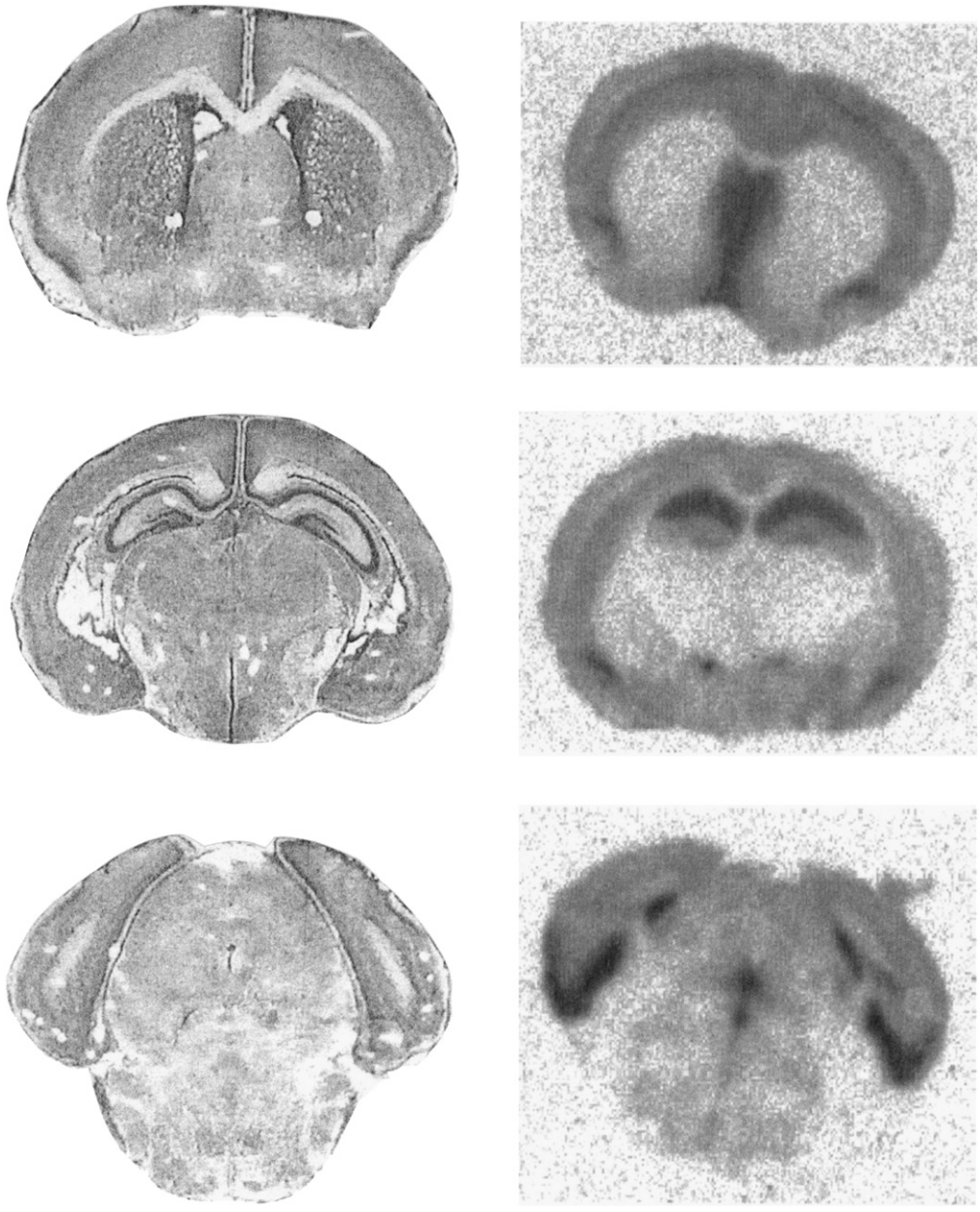

Fig. 1. Illustration of analyzed brain planes. The figure shows exemplary Nissl-stained brain slices and corresponding autoradiograms of weanlings visualizing the different planes (1–3) used for [^{3}H]8-OH-DPAT specific binding analysis.

in ABH weanlings ($p = 0.002$) as well as adults ($p = 0.001$) in the parietal cortex compared to ABG counterparts and for adult ABH mice in the cortical/medial amygdala ($p = 0.001$; in weanlings tendency only: $p = 0.2$) respective in the hippocampus ($p = 0.000$; in weanlings tendency only: $p = 0.055$) compared to ABG mice. No significant strain differences in 5-HT1A receptor binding can be observed in the dorsal raphe nucleus (weanlings: $p = 0.170$ and adults: $p = 0.065$).

4. Discussion

4.1. Age effects on 5-HT1A receptor binding in ABH and ABG mice

[^{3}H]8-OH-DPAT binding was very low at PND 1 in all brain regions analyzed. This is in line with Hillion et al. (1993) reporting very low 5-HT1A receptor mRNA concentrations in whole rat brain homogenates around birth. 5-HT1A receptor binding was high and reached levels comparable to that in adults in 3-week-old mice of both strains. A progressive increase in [^{3}H]5-HT, [^{3}H]8-OH-DPAT, and [^{125}J]-MPPI binding was already observed in the brains of rats and mice where adult levels were reached in the 3rd postnatal week (Daval et al., 1987; Gross et al., 2002; Uphouse and Bondy, 1981). So, the development of 5-HT1A receptor binding in young ABH and ABG mice is consistent to the data published for rats and mice elsewhere.

After weaning, 5-HT1A receptor binding develops differently in the brain regions analyzed. 5-HT1A receptor binding decreased during aging in the parietal cortex and dorsal raphe nucleus, but increased in the cortical/medial amygdaloid nuclei as well as in the CA1 field of the hippocampus. The 5-HT metabolism might be an important regulator for the development of the 5-HT1A receptor binding. In the cortex of mice, the 5-HT metabolism tended to increase between 6 and 12 weeks after birth, but in the hippocampus 5-HT metabolism strongly decreased (Rilke et al., 1998). This could explain our receptor data, where the cortical 5-HT1A receptor binding further decreased, but the hippocampal increased. Also, corticosterone is a strong negative regulator of 5-HT1A receptor gene expression, especially in the hippocampus, where its receptors are densely expressed (Wissink

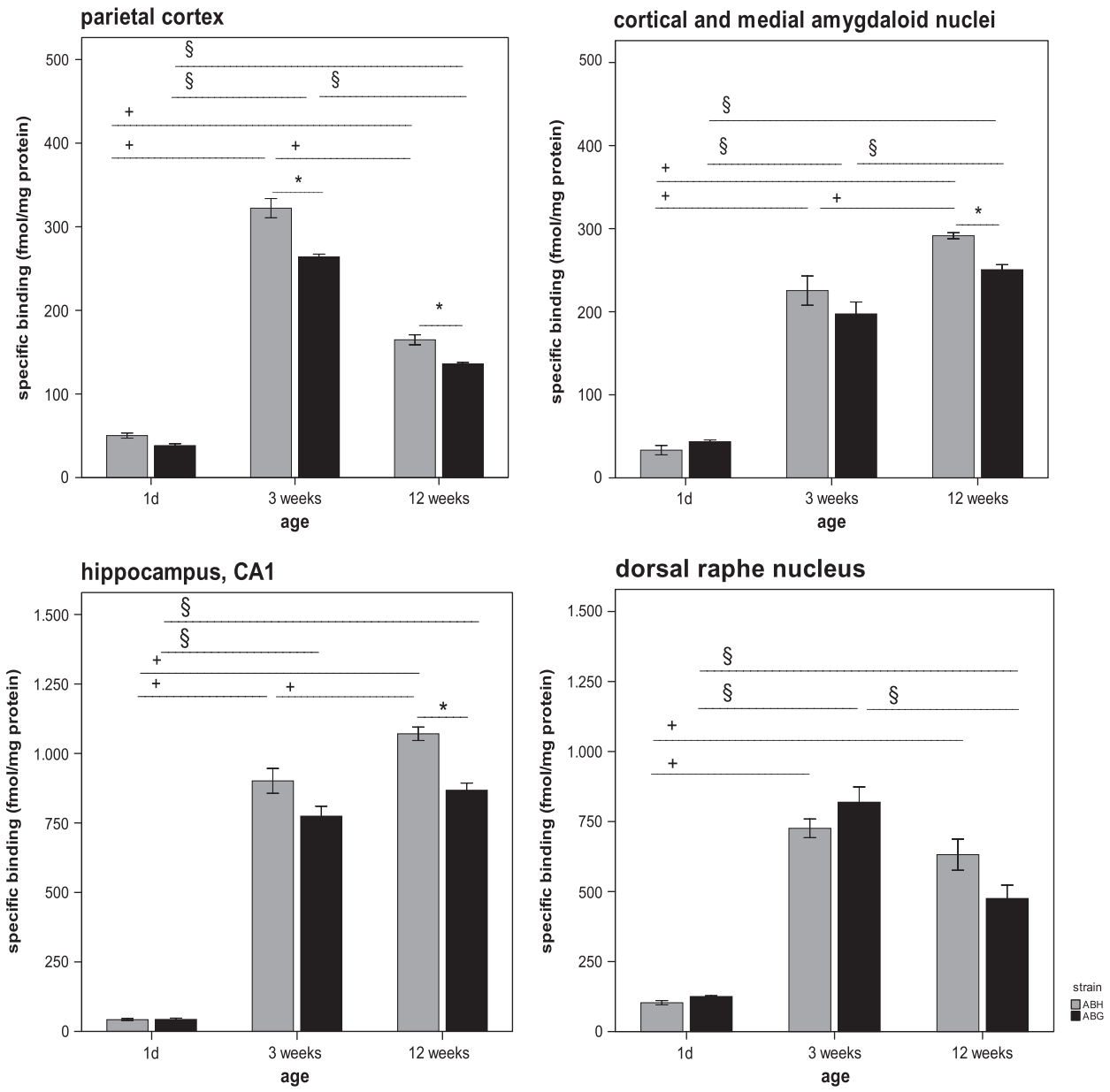

Fig. 2. Effects of age and strain on 5-HT1A receptor binding. Diagrams display [³H]8-OH-DPAT binding means +/−S.E.M. ($N = 4–6$) of 1-day-old, 3- respective 12-week-old ABH and ABG mice in fmol/mg protein. *Student's* t-tests were done for comparisons between strains and different ages. After *Bonferroni*-correction for multiple comparisons within one brain region, p was set and is presented as follows: strain differences * ≤0.016, age effects in ABH mice + ≤0.008, and age effects in ABG mice § ≤0.008.

et al., 2000). Though an essential influence of corticosterone on 5-HT1A receptor gene expression can be excluded in very young mice, because Schmidt et al. (2003) found very low basal corticosterone levels between birth and PND 12 of mice. Later on, corticosterone levels subsequently increase and hippocampal mineralo- as well as glucocorticoid receptors are detectable. So, the 5-HT system as well as the HPA-axis influences forebrain, especially hippocampal, 5-HT1A receptor expression around weaning. After weaning, serum corticosterone levels as well as faecal corticosterone metabolites decrease (Bielohuby et al., 2007; Touma et al., 2004). This might explain the higher 5-HT1A receptor binding in the corticosterone-sensitive hippocampus in 12-week-old AB mice.

Considering the significant interactions between age and strain in most of the brain regions analyzed, we found that the increases and decreases in 5-HT1A receptor binding during development are more pronounced in ABH mice in all forebrain regions, but less pronounced in the dorsal raphe nucleus compared to ABG mice. We assume that strain differences in CNS biochemistry (lower 5-HIAA concentrations in ABH vs. ABG mice) and blood corticosterone content (lower in ABH vs. ABG mice) observed in adult mice (Schiller et al., 2006) are crucial.

4.2. Strain effects on 5-HT1A receptor binding and their relation to behavior

ABH mice are highly active and impulsive as well as they become easily aggressive compared to the less active and never aggressive ABG mice (Schiller et al., 2006; Schneider et al., 1992). They differ also in corticosterone concentration, central nervous biochemistry as well as in 5-HT2A, but especially in the forebrain 5-HT1A receptor binding (Schiller et al., 2006). Forebrain 5-HT1A receptors are involved in the regulation of locomotion, exploration, and especially aggression. Three artificial mouse breeding lines (SAL-LAL, TA-TNA, and NC900-NC100) selected for either high or low aggression exist. Caramaschi et al. (2007) reported an across-strain comparison of the serotonergic

system in these mice. Highly aggressive mice had lower 5-HT and 5-HIAA levels in the prefrontal cortex and two out of these three aggressive strains displayed a higher sensitivity of 5-HT1A receptors especially at the postsynaptic site, which is in line with our results obtained in ABH mice. Another study analyzing mice of the short (SAL) vs. long attack latency (LAL) strain revealed also higher forebrain 5-HT1A receptor binding levels in the aggressive SAL mice similarly to what we have observed in ABH mice (Korte et al., 1996). Pharmacological studies with different 5-HT1A receptor agonists further support the relevance of 5-HT1A receptors in anxiety, locomotion (File and Gonzalez, 1996; Mignon and Wolf, 2002), and especially aggression (van der Vegt et al., 2001) regulation (for review, see: (De Vry, 1995)). But it is still a matter of debate if the somatodendritic (de Boer et al., 2000) or the postsynaptic (Sanchez and Hyttel, 1994; Sijbesma et al., 1991) localized 5-HT1A receptor causes the anti-aggressive effect of agents acting at the 5-HT1A receptor. Problematic are also their general influence on other behaviors as anxiety, locomotion, and social interaction. Data from 5-HT1A receptor knockout mice as well as transgenic mice over-expressing forebrain 5-HT1A receptors hint at a modulatory effect of forebrain 5-HT1A receptors in anxiety and locomotion (Bert et al., 2005; Bert et al., 2006; Gross et al., 2002; Zhuang et al., 1999). Aggression-relevant tests were only applied to 5-HT1A receptor knockout mice and preliminary data point at a lower aggression in these mice (Zhuang et al., 1999). The above-mentioned studies were the basis of our idea to assume trait marker qualities for the strain-specific 5-HT1A receptor binding profile. If so, strain differences in 5-HT1A receptor binding should appear early and should be consistent over time. In consequence, a relevance of the strain-specific 5-HT1A receptor binding for differences in locomotion and especially aggression that others and we have found in the two AB mice strains is to state (Schiller et al., 2006; Schneider-Stock and Epplen, 1995; Schneider et al., 1992). At birth, both AB mouse strains show comparable 5-HT1A receptor binding in the amygdala, hippocampus, and in the dorsal raphe. But the statistical analysis revealed a nearly significant difference in the parietal cortex where ABH mice already display a higher 5-HT1A receptor binding compared to ABG mice. It might be that in vitro autoradiography is not sensitive enough to detect small strain differences at this time-point since [^{3}H]8-OH-DPAT binding is very low. Further analyses using in situ hybridization or pooled brain homogenates could be useful in this regard.

However, as previously described for 12-week-old adults, we found already enhanced forebrain 5-HT1A receptor binding in 3-week-old ABH compared to ABG mice especially in the parietal cortex. So the strain-dependent difference in the forebrain 5-HT1A receptor binding develops definitely early in development. A genetic determination is likely, but so far, complex interactions between strain-specific genotypes and environment cannot be excluded. The maternal behavior could be especially essential for the development of the specific 5-HT1A receptor profile. Generally, we observed no significant strain differences in pup survival, litter size, and sex ratio during breeding. But we observed that ABH mothers spent clearly less time in the nest and with their pups (data not quantified). It is already known that a brief maternal deprivation of rat pups increased 5-HT1A receptor binding significantly in the amygdala (Vicentic et al., 2006), whereas one long deprivation session increased 5-HT1A receptor mRNA in the hippocampal CA1 region (Vazquez et al., 2002). It might be that a less intensive care by ABH mothers during the first weeks of live mimics short maternal deprivation episodes and causes an increase in forebrain 5-HT1A receptor binding as seen in ABH weanlings and adults with the known behavioral characteristics. Mixed-strain housing and cross-fostering are ideal to reveal gene-environment interactions. Both did not change the different vulnerability to isolation-induced aggression in ABH and ABG mice (Hoffmann et al., 1993). Therefore, the authors concluded an exclusive genetic basis for the differences in aggression. But it remains unclear, if the aggressive behavioral phenotype of ABH mice is indeed exclusively genetically determined since those mice were isolated for 2 weeks after artificial rearing. Further studies should clarify if a strain difference in maternal behavior is an important environmental factor for strain differences in 5-HT1A receptor binding. The quantitative analysis of maternal behavior (e.g. licking of pups, time spent in- and outside the nest) and again cross-fostering could be useful in this regard.

Also the influence of other already described differences in the neurobiology of these strains that we (Schiller et al., 2006) and others (Becker et al., 1991; Becker et al., 1997; Marashi et al., 2004; Prior et al., 2004) have described could be important for behavioral differences between the strains. Especially the analyses of Becker et al. (1991, 1997) are important since their strain comparison revealed differences in the level of systems mediating central inhibition, i.e. a less effective GABAergic but also a less sensitive opioidergic transmission in ABH compared to ABG mice. This could be functionally relevant besides the differences in the 5-HT system and the generally diametrically opposed results in forebrain noradrenaline concentrations and dopaminergic parameters measured basally and directly after a behavioral (resident-intruder-test) challenge (Schiller et al., 2006). We propose that a general difference in the balance of inhibitory/excitatory influences on the brain network lead to a higher impulsivity in ABH compared to ABG mice as can be seen from a stronger behavioral responsiveness to environmental stimuli expressed by hyperactivity or tail rattling behavior and biting attacks that were only described in ABH mice (Schiller et al., 2006; Schneider et al., 1992).

In summary, we observed that strain differences in forebrain 5-HT1A receptor binding in ABH and ABG mice develop during the first 3 postnatal weeks and remain stable afterwards. So, trait-like qualities for the strain-dependent 5-HT1A receptor binding pattern are demonstrated. Supported by the mentioned literature, we suppose especially the 5-HT1A receptor binding differences beside those in inhibitory/excitatory balances as crucial for the observed strain differences in the behavioral responsiveness to environmental demands independently if they are social or non-social. Early pharmacological manipulation by the application of 5-HT1A receptor ligands in pups should be done to further elucidate the impact of 5-HT1A receptors for behavioral differences observed later on in adult ABH and ABG mice.

References

Becker A, Ruethrich HL, Schneider R, Grecksch G, Matthies H. Pharmacological effects on two inbred substrains of AB mice. Pharmacol Biochem Behav 1991;38:471–3.

Becker A, Schroder H, Brosz M, Grecksch G, Schneider-Stock R. Differences between two substrains of AB mice in the opioid system. Pharmacol Biochem Behav 1997;58:763–6.

Bert B, Dere E, Wilhelmi N, Kusserow H, Theuring F, Huston JP, et al. Transient overexpression of the 5-HT1A receptor impairs water-maze but not hole-board performance. Neurobiol Learn Mem 2005;84:57–68.

Bert B, Fink H, Hortnagl H, Veh RW, Davies B, Theuring F, et al. Mice over-expressing the 5-HT(1A) receptor in cortex and dentate gyrus display exaggerated locomotor and hypothermic response to 8-OH-DPAT. Behav Brain Res 2006;167:328–41.

Bielohuby M, Herbach N, Wanke R, Maser-Gluth C, Beuschlein F, Wolf E, et al. Growth analysis of the mouse adrenal gland from weaning to adulthood: time- and gender-dependent alterations of cell size and number in the cortical compartment. Am J Physiol Endocrinol Metab 2007;293:E139–46.

Caramaschi D, de Boer SF, Koolhaas JM. Differential role of the 5-HT1A receptor in aggressive and non-aggressive mice: an across-strain comparison. Physiol Behav 2007;90:590–601.

Daval G, Verge D, Becerril A, Gozlan H, Spampinato U, Hamon M. Transient expression of 5-HT1A receptor binding sites in some areas of the rat CNS during postnatal development. Int J Dev Neurosci 1987;5:171–80.

de Boer SF, Lesourd M, Mocaer E, Koolhaas JM. Somatodendritic 5-HT(1A) autoreceptors mediate the anti-aggressive actions of 5-HT(1A) receptor agonists in rats: an ethopharmacological study with S-15535, alnespirone, and WAY-100635. Neuropsychopharmacology 2000;23:20–33.

De Vry J. 5-HT1A receptor agonists: recent developments and controversial issues. Psychopharmacology (Berl) 1995;121:1-26.

File SE, Gonzalez LE. Anxiolytic effects in the plus-maze of 5-HT1A-receptor ligands in dorsal raphe and ventral hippocampus. Pharmacol Biochem Behav 1996;54:123–8.

Franklin KBJ, Paxinos G. The mouse brain in stereotaxic coordinates. San Diego, CA: Academic Press; 1997.
Gross C, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, et al. Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. Nature 2002;416:396–400.
Hillion J, Milne-Edwards JB, Catelon J, de Vitry F, Gros F, Hamon M. Prenatal developmental expression of rat brain 5-HT1A receptor gene followed by PCR. Biochem Biophys Res Commun 1993;191:991–7.
Hoffmann HJ, Schneider R, Crusio WE. Genetic analysis of isolation-induced aggression. II. Postnatal environmental influences in AB mice. Behav Genet 1993;23:391–4.
Korte SM, Meijer OC, de Kloet ER, Buwalda B, Keijser J, Sluyter F, et al. Enhanced 5-HT1A receptor expression in forebrain regions of aggressive house mice. Brain Res 1996;736:338–43.
Marashi V, Barnekow A, Sachser N. Effects of environmental enrichment on males of a docile inbred strain of mice. Physiol Behav 2004;82:765–76.
Mignon L, Wolf WA. Postsynaptic 5-HT(1A) receptors mediate an increase in locomotor activity in the monoamine-depleted rat. Psychopharmacology (Berl) 2002;163: 85–94.
Paxinos G, Ashwell KWS, Törk J. Atlas of the developing rat nervous system. San Diego, California: Academic Press; 1994.
Popova NK. From genes to aggressive behavior: the role of serotonergic system. BioEssays 2006;28:495–503.
Prior H, Schwegler H, Marashi V, Sachser N. Exploration, emotionality, and hippocampal mossy fibers in nonaggressive AB/Gat and congenic highly aggressive mice. Hippocampus 2004;14:135–40.
Rilke O, Freier D, Jaehkel M, Oehler J. Dynamic alterations of serotonergic metabolism and receptors during social isolation of low- and high-active mice. Pharmacol Biochem Behav 1998;59:891–6.
Sanchez C, Hyttel J. Isolation-induced aggression in mice: effects of 5-hydroxytryptamine uptake inhibitors and involvement of postsynaptic 5-HT1A receptors. Eur J Pharmacol 1994;264:241–7.
Schicknick H, Hoffmann HJ, Schneider R, Crusio WE. Genetic analysis of isolation-induced aggression in the mouse. III. Classical cross-breeding analysis of differences between two closely related inbred strains. Behav Neural Biol 1993;59:242–8.
Schiller L, Donix M, Jaehkel M, Oehler J. Serotonin 1A and 2A receptor densities, neurochemical and behavioural characteristics in two closely related mice strains after long-term isolation. Prog Neuropsychopharmacol Biol Psychiatry 2006;30: 492–503.
Schmidt MV, Enthoven L, van der Mark M, Levine S, de Kloet ER, Oitzl MS. The postnatal development of the hypothalamic-pituitary-adrenal axis in the mouse. Int J Dev Neurosci 2003;21:125–32.
Schneider-Stock R, Epplen JT. Congenic AB mice: a novel means for studying the (molecular) genetics of aggression. Behav Genet 1995;25:475–82.
Schneider R, Hoffmann HJ, Schicknick H, Moutier R. Genetic analysis of isolation-induced aggression. I. Comparison between closely related inbred mouse strains. Behav Neural Biol 1992;57:198–204.
Sijbesma H, Schipper J, de Kloet ER, Mos J, van Aken H, Olivier B. Postsynaptic 5-HT1 receptors and offensive aggression in rats: a combined behavioural and autoradiographic study with eltoprazine. Pharmacol Biochem Behav 1991;38:447–58.
Staats J. Standardized nomenclature for inbred strains of mice: eighth listing. Cancer Res 1985;45:945–77.
Touma C, Ambree O, Gortz N, Keyvani K, Lewejohann L, Palme R, et al. Age- and sex-dependent development of adrenocortical hyperactivity in a transgenic mouse model of Alzheimer's disease. Neurobiol Aging 2004;25:893–904.
Uphouse LL, Bondy SC. The maturation of cortical serotonin binding sites. Brain Res 1981;227:415–7.
van der Vegt BJ, de Boer SF, Buwalda B, de Ruiter AJ, de Jong JG, Koolhaas JM. Enhanced sensitivity of postsynaptic serotonin-1A receptors in rats and mice with high trait aggression. Physiol Behav 2001;74:205–11.
Vazquez DM, Eskandari R, Zimmer CA, Levine S, Lopez JF. Brain 5-HT receptor system in the stressed infant rat: implications for vulnerability to substance abuse. Psychoneuroendocrinology 2002;27:245–72.
Vicentic A, Francis D, Moffett M, Lakatos A, Rogge G, Hubert GW, et al. Maternal separation alters serotonergic transporter densities and serotonergic 1A receptors in rat brain. Neuroscience 2006;140:355–65.
Wissink S, Meijer O, Pearce D, van Der Burg B, van Der Saag PT. Regulation of the rat serotonin-1A receptor gene by corticosteroids. J Biol Chem 2000;275:1321–6.
Zhuang X, Gross C, Santarelli L, Compan V, Trillat AC, Hen R. Altered emotional states in knockout mice lacking 5-HT1A or 5-HT1B receptors. Neuropsychopharmacology 1999;21:52S–60S.