Selectively Bred Rodents as Models of Depression and Anxiety

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Abstract Stress related diseases such as depression and anxiety have a high degree of co morbidity, and represent one of the greatest therapeutic challenges for the twenty-first century. The present chapter will summarize existing rodent models for research in psychiatry, mimicking depression- and anxiety-related diseases. In particular we will highlight the use of selective breeding of rodents for extremes in stress-related behavior. We will summarize major behavioral, neuroendocrine and neuronal parameters, and pharmacological interventions, assessed in great detail in two rat model systems: The Flinders Sensitive and Flinders Resistant Line rats (FSL/FRL model), and rats selectively bred for high (HAB) or low (LAB) anxiety related behavior (HAB/LAB model). Selectively bred rodents also provide an excellent tool in order to study gene and environment interactions. Although it is generally accepted that genes and environmental factors determine the etiology of mental disorders, precise information is limited: How rigid is the genetic disposition? How do genetic, prenatal and postnatal influences interact to shape adult disease? Does the genetic predisposition determine the vulnerability to prenatal and

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postnatal or adult stressors? In combination with modern neurobiological methods, these models are important to elucidate the etiology and pathophysiology of anxiety and affective disorders, and to assist in the development of new treatment paradigms.

Keywords Animal models · Selective breeding · Depression · Anxiety

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1 Introduction

It has been estimated that 127 million Europeans out of a population of 466 million currently live with a brain disorder, with total annual costs (of brain disorders in Europe) of €386 billion in 2004 (Andlin-Sobocki et al. 2005). Of these, mental disorders constitute about 60% of the total costs reflecting the large socioeconomic burden of these diseases. These numbers greatly emphasize the importance of developing new strategies in treating mental disorders.

Stress-related diseases such as depression and anxiety, having a high degree of co-morbidity, represent one of the greatest therapeutic challenges for the twenty-first century. Although it is generally accepted that genes and environmental factors determine depression, precise information is limited: How rigid is the genetic disposition? How do genetic, pre- and post-natal influences interact to shape adult depression? Does the genetic predisposition determine the vulnerability to pre- and post-natal or adult stressors?

When depression, and in some degree anxiety, precipitates, the dominating etiological hypotheses have focused at a dysregulation in the serotonergic and noradrenergic system. This is emphasized by the mechanism of action of the

currently marketed antidepressants, which almost exclusively act by direct modulation of these two systems. Unfortunately, the efficacy of the presently clinically used antidepressant drugs are low, only approximately 30–35% after subtracting the placebo effects. Thus, there exists a major unmet medical need, the resolution of which is contingent on elucidating the disease etiology and pathogenesis.

Therefore, good model systems are needed to answer fundamental neurobiological questions and to predict responses to novel therapeutic agents. Animal models can be assessed on the basis of five major criteria (Willner 1984; Geyer and Markou 1995): face validity (how well the model resembles the disease/condition), construct validity (how well the model is consistent with theoretical rationale), etiological validity (how identical are the etiologies of the disease (phenomenon) in the animal model and in humans), convergent/discriminant validity (the degree to which a test correlates with other tests that attempt to measure the same construct/the degree to which a test measures aspects of a phenomenon that are different from other aspects of the phenomenon that other tests assess (Campbell and Fiske 1959), and predictive validity (how well the model responds favorably to clinically established drugs). An optimal model fulfills all the criteria. However, a model can even be useful, even if not all conditions are met (Geyer and Markou 1995).

Genetic selection for behavioral and other phenotypic characteristics is a core feature in evolution, and crucial for survival of any species. Selective breeding is the process of breeding plants or animals for particular genetic traits, which is desired by the researcher. Selective breeding has proven to be a valuable tool in the advancement of science. In fact, one of the most commonly used animals in laboratory research, the Wistar rat, may be considered—in the strict terms of selective breeding—an example of selective breeding. This strain was developed at the Wistar Institute in 1906 for use in biological and medical research, and it was the first rat strain developed to serve as a model organism at a time when biological laboratories primarily used mice (Clause 1998; Lindsay and Baker 2006). Several of the laboratory rat strains used today originate from the original Wistar colony established by Donaldson, Greenman, and King (Clause 1998; Lindsay and Baker 2006).

With this development, it is therefore not surprising that several selectively bred animal models also have been established in neuroscience and psychiatric research.

Selectively bred models are essential for studying underlying mechanisms of the disease and have been established for various psychopathological entities/phenotypes, as it appears from Table 1.

The present chapter will highlight the use of selective breeding in order to establish animal models for research in psychiatry, with special focus on depression and anxiety disorders. We will highlight two rat models: the Flinders Sensitive and Flinders Resistant Line (FSL/FRL) and rats selectively bred for high (HAB) or low (LAB) anxiety-related behavior (HAB/LAB model). A very brief description of other existing selectively bred rodents, modeling depression and anxiety is also given. For the remaining models on e.g., schizophrenia and epilepsy, a detailed description can be found in the references listed in Table 1.

Table 1 Overview of some selectively bred animal models

Disease/phenotype	Model	Species	Reference
ADHD/impulsivity	Naples high/low excitability (NHE/NLE)	Rats	Sadile et al. (1988); Cerbone et al. (1993); Viggiano et al. (2003)
Aggression	Novosibirsk	Rats	Naumenko et al. (1989)
	Turku	Mice	Sandnabba (1996)
	SAL/LAL	Mice	van Oortmerssen and Bakker (1981)
Alcoholism	HAD/LAD	Rats	Li et al. (1993); Li and Lumeng (1977); Murphy et al. (2002)
	Fawn hooded (FH/Wjd)	Rats	Rezvani et al. (1990), (1991), (2007)
Anxiety	Floripa H and L	Rats	Ramos et al. (1998), (2002), (2003)
	HAB/LAB	Rats	*See Main Text* Liebsch et al. (1998b); Landgraf and Wigger (2002); Landgraf et al. (2007)
	HAB/LAB	Mice	Kessler et al. (2011); Kromer et al. (2005)
	Maudsley MRS/MNS	Rats	Broadhurst (1960); Blizard and Adams (2002)
	High/low avoidance: syracuse SHA/BRU and SLA/Bru Roman HA/LA	Rats	Brush et al. (1985), (1989); Brush (2003)
Depression	WKY	Rats	Pare and Redei (1993); Lahmame et al. (1997); Will et al. (2003)
	FSL/FRL	Rats	*See Main Text* Overstreet et al. (2005); Overstreet (1986)
	SwLo/SwHi	Rats	West and Weiss (1998b)
	LR/HR	Mice	Touma et al. (2008)
	cLH/cNLH	Rats	Vollmayr and Henn (2001); Vollmayr et al. (2001)
	Fawn hooded (FH/Wjd)	Rats	Rezvani et al.(2002)
Epilepsy	WAG/Rij	Rats	Van Luijtelaar and Coenen (1986), (1989); Coenen and Van Luijtelaar (2003)
	Gaers	Rats	Vergnes et al. (1982); Marescaux et al. (1992); Marescaux et al. (1984)
Schizophrenia	APO-SUS/APO-UNSUS	Rats	Ellenbroek and Cools (2000); Costall and Naylor (1973); Ellenbroek and Cools (2002)

Table 2 Symptoms in depressed individuals which can be modeled in FSL rats

Symptom/activity	Patients	FSL rats
Suicidal ideas	Frequent	Cannot be modeled
Activity	Psychomotor retardation	Reduced bar pressing for rewards
Anhedonia	Yes	Yes (following stress)
Appetite	Reduced	Reduced
Weight	Weight loss	Lower body weight
Cognitive performance	Reduced	Reduced/normal (dependent on test)
REM Sleep	Elevated	Elevated
Anxiety	Not a core feature	No anxiety
HPA axis dysregulation	Yes	Yes
Treatment response (see text)	Yes	Yes
Killer T-cell activity	Reduced	Reduced
Cardiovascular morbidity	Increased	Increased

2 Selectively Bred Models on Depression

2.1 The Flinders Sensitive and Resistant Line Rat

The Flinders Line rats were established by selective breeding for differential responses to the anticholinesterase agent, diisopropyl fluorophosphate (DFP), at Flinders University in Adelaide, Australia. The original rationale was to breed a rat strain that would be genetically resistant to irreversible anticholinesterase agents, DFP. However, the selective breeding of Sprague–Dawley (SD) rats, resulted in a line more sensitive to DFP, the Flinders Sensitive Line (FSL), whereas the Flinders Resistant Line (FRL) rats were not more resistant than an outbred control (Overstreet et al. 1979; Russell et al. 1982). Being less tolerant to DFP, the FSL rat were also found to be more sensitive to drugs targeting the cholinergic system, in particular effects of directly acting muscarinic receptor agonists (Russell and Overstreet 1987; Overstreet and Russell 1982; Overstreet 1986) and to have more muscarinic receptors in several brain regions (Overstreet and Russell 1984).

As it also was reported that depressed individuals were more sensitive to cholinergic agonists than normal controls, defined by behavior, neuroendocrine measures and sleep (Janowsky et al. 1980, 1994; Risch et al. 1981), it was suggested that the FSL rat might be a model for depression.

Today there are now breeding colonies of the FSL rats in Australia, Canada, Denmark, Greece, Israel, Mexico, South Africa, Sweden and United States.

2.1.1 Key Features of the FSL Rat Depression Model

As mentioned, the FSL line phenotypically resembles a number of depression symptoms and has been a useful tool to elucidate the endophenotype of depression. Indeed, extensive work has demonstrated that many of the core symptoms of

depression can be reproduced in the FSL strain; the more salient characteristics are shown in Table 1.

Depression-Related Behavior

Several observations of the unmotivated and motivated behavior of the FSL rat suggest that it exhibits psychomotor retardation, a key behavioral characteristic of depressed individuals (Lecrubier 2006). In particular, the FSL rat is less active in a novel open field (Overstreet and Russell 1982; Overstreet et al. 1986), bar-presses at a low rate for water or food reward (Overstreet and Russell 1982; Bushnell et al. 1995), and does not complete food-motivated nonmatching- to-sample learning trials in a timely manner (Bushnell et al. 1995).

Importantly, the FSL rats show increased immobility in the forced swim test (FST), which is the prototypic screening tool for depression-like behavior in rodents (Overstreet and Russell 1982; Schiller et al. 1992; El Khoury et al. 2006). Especially of interest for the predictive validity of the model, these behaviors are reversible by chronic but not acute treatment with antidepressants.

Anhedonia, the inability to experience pleasure, is often regarded as a core symptom of depression. Interestingly, under basal conditions the FSL compared to FRL rats did not show signs of anhedonia, and signs of anhedonia were only found when FSL rats were exposed to chronic mild stress (Pucilowski et al. 1993; Matthews et al. 1996), supporting this model as being a candidate for Gene × Environment studies. We have replicated these findings, and found that group housed FSL rats display a higher level of anhedonia following chronic mild stress exposure, when compared with the FRL rats (Mathé et al. unpublished results).

A reduction in appetite is a classical symptom seen in most depressed individuals, while an increase in appetite and weight gain is observed in fewer. Appetite and food intake in the FSL and FRL rats has not been studied in detail, but the FSL rat weighs less than the FRL rat and in a recent study the FSL were found to consume less food than FRL (Abildgaard et al. 2010). It, therefore, appears that the FSL rats have a decreased appetite thus resembling the reduced appetite in depressed individuals.

Anxiety-Related Behavior

Anxiety is not considered a core feature of depression, but there exist a high degree of co-morbidity of anxiety with depression. Therefore, the behavior of FSL was examined in the classical test of anxiety-like behavior, the elevated plus maze (EPM), which is an unconditioned test for anxiety in rodents, and works by creating a conflict between an animal's exploratory drive and its fear of open and brightly-lit areas. Under baseline conditions no differences were discovered between the FSL and FRL lines (Overstreet et al. 1995). Treatment with a benzodiazepine exerted a comparable anxiolytic effect in both FSL and FRL rats

and did not differentiate between the two strains (Schiller et al. 1991; Mathé et al. unpublished data).

However, our own recent results demonstrated that FSL rats had a reduced level of unconditioned anxiety on the EPM compared to the FRL rats (Abildgaard et al. 2010). Specifically, the FSL spent more time on the open arms and had a higher level of full entries onto open arms. Similar findings have been described in young FSL rats compared to SD rats (Braw et al. 2006). It is, however, of interest to note that FSL rats did exhibit some anxiogenic behavior in the social interaction task (Overstreet et al. 2004b), which may reflect enhanced social anxiety, or alternatively, reduced social motivation and social withdrawal.

Taken together, as anxiety does not seem to be a prominent feature of the FSL strain, the FSL rats seem to be a model for depression without comorbidity of anxiety. However, as anxiety can be judged from multiple paradigms, further studies are warranted.

Cognition

Cognitive disturbances in depressed individuals can involve both learning difficulties and memory loss. Most learning and memory studies on FSL rats used foot shock as the motivating stimulus, where the FSL rat show greater difficulty in acquiring a shock-motivated, active avoidance task (Overstreet et al. 1990). On the other hand, the FSL rat exhibited normal memory of a shock-motivated passive avoidance task (Overstreet et al. 1992; Russell et al. 1982). Also in a food-motivated task similar completion rates between the FSL and the FRL were obtained, achieved by reducing the size of the food pellet in the FSL rats (Bushnell et al. 1995). Although the FSL rats did not perform this task as rapidly as the FRL rats, they chose the correct bar just as efficiently (Bushnell et al. 1995). Thus, there is no definitive evidence for cognitive disturbances in the FSL rats under basal conditions, which is further underlined by a recent study from Aarhus, where the FSL show similar spatial memory abilities as the FRL in the Morris Water Maze (Wegener et al. unpublished).

Pain

Affective disorders have been repeatedly linked with alterations in thermal and visceral pain perception (Haug et al. 2004; Vedolin et al. 2009; Robinson et al. 2009). However, only a limited number of studies have been carried out in the FSL model. In a model with partial denervation of the sciatic nerve (PSL model), which produces a chronic decrease in touch and heat withdrawal thresholds (allodynia) and an increased response to noxious mechanical and heat stimuli (hyperalgesia, Fujioka et al. 2001; Fumagalli et al. 2007), the FSL rats expressed significantly lower levels of tactile allodynia and less heat hyperalgesia following PSL injury compared to SD rats

(Shir et al. 2001). These studies have been carried out using a denervation model, and no results for basal pain parameters are available.

Sleep Patterns

Sleeping disorders are very closely associated with depressive disorders, with both insomnia and hypersomnia being observed. Two pronounced changes associated with depression are increases in rapid eye movement (REM) sleep and decreases in slow wave sleep (Jindal et al. 2002; Thase et al. 1995; Benca 1996; Benca et al. 1992; Adrien 2002). Basal sleep recordings in the FSL have demonstrated that the FSL rat exhibited a reduced latency to—and greater amount of REM sleep than the FRL rats (Benca et al. 1996; Shiromani et al. 1991), with no differences in slow wave sleep patterns. Thus, the FSL rat resembled depressed individuals with regard to the elevated REM sleep, but not with regard to the reduced slow wave sleep (Jindal et al. 2002; Benca et al. 1992).

Hypothalamic-Pituitary Adrenal Axis

Distinct changes in the Hypothalamic-Pituitary Adrenal (HPA) axis reactivity and cortisol levels in severe depression (melancholia) are well documented (Keck and Holsboer 2001). However, studies in the FSL/FRL model are conflicting: Whereas no differences in corticosterone levels under basal conditions or in response to a chronic mild stressor have been found (Ayensu et al. 1995), in another study, the FSL rats had significantly lower plasma ACTH concentrations compared with the FRL, but still with no differences in plasma corticosterone concentrations between the two groups (Owens et al. 1991). In the brain, it was found that the density of anterior pituitary CRF receptor binding sites was elevated in the FSL rats compared with the FRL (Owens et al. 1991).

This finding is further substantiated by later studies, where FSL and FRL, were subjected to 1 h acute restraint and the effects of the stress exposure, including possible strain specific changes were studied (Zambello et al. 2008). Under basal conditions, no significant differences between FSL and FRL rats in the CRH mRNA expression were found. However, an upregulation of the CRH mRNA hybridization signal was detected in the central amygdala of the stressed FRL, compared to the non-stressed FRL rats (Zambello et al. 2008). Following these findings, it was hypothesized that, since a hypoactive mechanism of response to stressful stimuli in the FSL rats was present, lack of amygdala CRH activation following stress could suggest a subtype of allostatic load, which may alter the interpretation of environmental stimuli by FSL rats and consequently influence their behavioral response to stressful situations (Zambello et al. 2008). However, these suggestions require further examinations.

Monoamine Metabolism

The monoaminergic hypothesis of depression (Schildkraut 1965) suggests that there are distinct abnormalities of the serotonergic system in depressed individuals, although several inconsistencies exist. For example, both serotonergic $5HT_{1A}$ receptor overactivity (Arango et al. 1995) as well as $5HT_2$ receptor underactivity have been reported (Mikuni et al. 1991).

In the FSL, several differences in the serotonin synthesis, $5HT_{1A}$ receptor sensitivity and the density of the serotonin transporter were found compared to the FRL strains (Overstreet et al. 1994; Kanemaru et al. 2009; Nishi et al. 2009; Kovacevic et al. 2010). However, whether these abnormalities are comparable to those seen in depressed individuals are not known, and there are some data suggesting inverse pharmacological responses in FSL rats and depressed individuals. For example, studies have shown that the FSL rats are more sensitive to the hypothermic effects of 5-HT1A receptor agonists (Wallis et al. 1988; Overstreet et al. 1994), but depressed individuals are usually less sensitive to these effects of similar agents (Lesch 1991). Moreover, in depressed individuals, both increases (Reddy et al. 1992), decreases (Asberg et al. 1984) or no changes (Roy et al. 1985) in the serotonin metabolite 5-hydroxy-indoleacetic acid (5-HIAA) in cerebrospinal fluid have been reported. How this may relate to the FSL model remains to be established.

The psychomotor retardation and anhedonia-like features following chronic mild stress (CMS) in the FSL rats may suggest the dopaminergic system to be involved. This has been supported by a few studies on dopamine metabolism and release from selected brain regions of FSL rats (Zangen et al. 2001; Yadid et al. 2001), and in behavioral responses to dopaminergic agents (Crocker and Overstreet 1991). However, it is not clear how these findings can be translated to human pathology.

Nitric Oxide Signaling

The atypical neurotransmitter nitric oxide (NO) possesses both neuroprotective and neurodestructive properties (Dawson and Dawson 1996; McCaslin and Oh 1995). Nitric oxide has been implicated in the psychopathology of depression, as postmortem studies on brains from the Stanley Consortium (Bethesda, MD, USA) have demonstrated that patients suffering from depression have an increase in NO synthase-immunoreactivity in the CA1 hippocampal area (Oliveira et al. 2008). By virtue of its unpaired electron, NO promotes the formation of free radicals and has been linked to various neurodegenerative processes (Ischiropoulos and Beckman 2003). Drugs that affect the major NO pathways have also been shown to possess antidepressant-like properties (Wegener and Volke 2010), and antidepressants have been shown to affect the NO signaling (Wegener et al. 2003). Investigation of NO signaling in the FSL rats did not reveal any baseline FSL–FRL differences in hippocampal constitutive NO synthase (cNOS) activity and neuronal nitric oxide

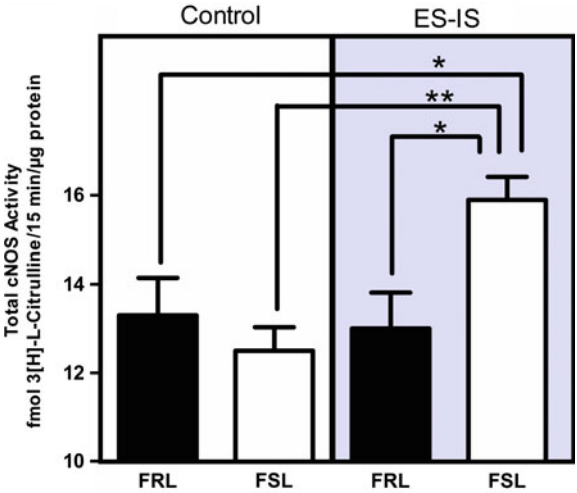

Fig. 1 Hippocampal constitutive nitric oxide synthase (cNOS) activity data under basal conditions [FSL ($n = 8$), FRL ($n = 7$)], and following escapable stress/inescapable stress (ES–IS) [FSL ($n = 8$), FRL ($n = 7$)]. Following ES–IS, cNOS activity is significantly elevated in FSL rats compared to unstressed FSL controls (** $p < 0.005$) and versus pre- and post-stress FRL animals (* $p < 0.05$). Pre- and post-stress activity levels for FRL rats did not differ from one another. Values shown are means + S.E.M. Reprinted from (Wegener et al. 2010) with permission. © Cambridge University Press

synthase (nNOS) protein levels. However, following exposure to stress in the escapable stress/inescapable stress paradigm, the FSL strain showed a larger activation of the cNOS system (Fig. 1), confirming the NMDA–NO cascade as an important vulnerability factor in the depression-like phenotype of the FSL rat (Wegener et al. 2010). Furthermore, several distinct agents affecting NO synthesis have also been shown to be effective antidepressants in the FSL (Wegener et al. unpublished observations, see Table 3).

Neuropeptides

Neuropeptide Y (NPY) is one of the most abundant peptides in the mammalian brain, interacting with the noradrenaline, serotonin and dopamine systems with effects on multiple brain functions. Several findings suggest that NPY plays an important role in the pathophysiology of depression and anxiety (Mathe et al. 2007; Heilig 2004).

Studying NPY in FSL has revealed marked similarities between vicissitudes of NPY in the rat depression models and human subjects. Thus, we have shown decreased NPY levels in the hippocampus of the FSL rats (Jimenez-Vasquez et al. 2000), and NPY protein and mRNA were found reduced in the CA1-2 regions and the dentate gyrus of FSL rats compared with FRL (Jimenez-Vasquez et al. 2000).

Table 3 Effect of some antidepressants (common and experimental), in the forced swim test (FST) in FSL (See also Overstreet et al. (2005); and Overstreet (1993))

Class	Drug	Response in FST	References
TCA	Desipramine	+	Overstreet et al. (2004b); Overstreet and Griebel (2004); Overstreet et al. (2010a); Overstreet et al. (2004a); Overstreet et al. (2008)
	Imipramine	+	(Schiller et al. (1992); Liebenberg et al. (2010)
	Nortryptyline	+	Petersen et al. (2009)
NaSSA	Nefazodone	+	Dremencov et al. (2004)
SSRI	Citalopram	+	Overstreet et al. (2004b)
	Escitalopram	+	El Khoury et al. (2006); Wegener et al. (unpublished)
	Paroxetine	+	Zangen et al. (2001); Zangen et al. (2002); Zangen et al. (1999), (1997)
	Sertraline	+	Pucilowski and Overstreet (1993)
	Fluoxetine	+	Overstreet and Griebel (2004); Overstreet et al. (2004a); Overstreet et al. (2008)
NOS inhibitors	Methylene blue	+	(Wegener et al. (unpublished)
	L-NAME	+	(Wegener et al. (unpublished)
	7-Nitroindazole	+	(Wegener et al. (unpublished)
NPY R5 antagonist	Lu AA33810	+	Walker et al. (2009)
CRF antagonist	CP-154,526	–	Overstreet et al. (2004b)
	SSR125543	+	Overstreet and Griebel (2004)
NK2 antagonists	Saredutant	+	Overstreet et al. (2010b)
Melatonin antagonists	S 20304	+	Overstreet et al. (1998)
PDE inhibitors	Rolipram	+	Overstreet et al. (1989)
	Sildenafil	+ (together with atropine)	Liebenberg et al. (2010)
Miscellaneous	ECS	+	Jimenez-Vasquez et al. (2007); Wegener et al. (unpublished)
	Tianeptine	+	Wegener et al. (unpublished)
	Ketamine	+	Wegener et al. (unpublished)
	Exercise	+	Bjornebekk et al. (2005)
	Nerve growth factor	+	Overstreet et al. 2010a)
	Nemifitide	+	Overstreet et al. (2004a)
	Amibegron	+	Overstreet et al. (2008)
	Lu AA21004	+	Mørk et al. (2012)
	Inositol	+	Einat et al. (2002)

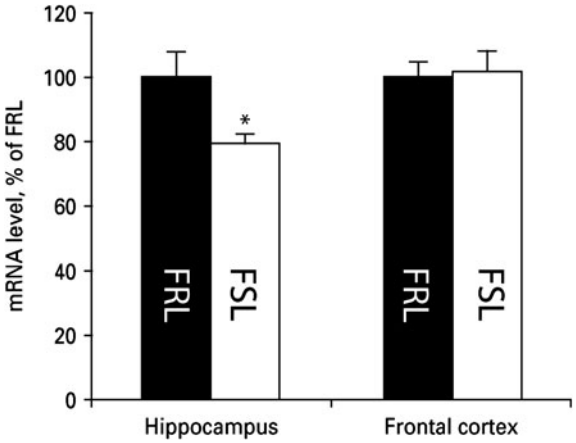

Fig. 2 Messenger RNA samples from hippocampus and frontal cortex of FSL (%; $n = 9$) and FRL (&; $n = 9$) rats were used for quantification of the expression levels of BDNF using real-time qPCR. Values for each individual were normalized with the geometric mean of the reference genes Ywhaz and Hmbs in the hippocampus and Ywhaz and Actb in the frontal cortex. Plotted data show mean group values + S.E.M. of mRNA expression as % of FRL rats. * Indicates significant between-group differences ($p < 0.05$). Reprinted from (Elfving et al. 2010a) with permission. © Cambridge University Press

In contrast, local NPY-Y1 receptor binding was increased, indicating functional significance of the changes in NPY availability (Jimenez-Vasquez et al. 2000a, 2000b; Husum et al. 2001; Caberlotto et al. 1999; Mathe et al. 2007).

Consistent with these data are the findings that antidepressants, lithium and ECS, all increase NPY expression in selected brain regions, and that the increases are larger in the FSL compared with the FRL strain (Husum et al. 2003; Husum et al. 2001; Jimenez Vasquez et al. 2000; Jimenez-Vasquez et al. 2007). For instance, reduced NPY levels in the CSF of depressed patients and altered NPY and NPY receptors mRNA expression in post-mortem brains have been shown (Widdowson et al. 1992; Olsson et al. 2004; Hou et al. 2006; Heilig 2004; Caberlotto et al. 1999; Caberlotto and Hurd 2001). Conversely, increased NPY concentrations in CSF following successful treatment of depressed in-patients with citalopram or ECT have been reported (Nikisch and Mathe 2008; Nikisch et al. 2005).

Neurotrophic Factors

Several studies have found decreased serum or plasma brain-derived neurotrophic factor (BDNF) levels in depressed patients, and a positive correlation between BDNF reduction and the severity of the disease has also been observed (Shimizu et al. 2003; Karege et al. 2002, 2005; Aydemir et al. 2006). Moreover, in

post-mortem hippocampal tissue, increased levels of BDNF immunoreactivity have been reported in subjects treated with antidepressants compared to untreated subjects (Chen et al. 2001). These findings constitute the rationale for studying BDNF also in the FSL model of depression. In a recent study from Aarhus, BDNF expression in the hippocampus was significantly decreased in the FSL compared with FRL rats (Fig. 2), while no differences were found in the frontal cortex or CSF (Elfving et al. 2010a). Contraintuitively, BDNF levels in serum and whole blood of the FSL rats were significantly increased compared with FRL rats (Elfving et al. 2010a). Whether this finding is relevant, or a peculiarity of the FSL, remains to be fully established. However, recent studies underline that multiple factors must be taken into consideration when correlating serum BDNF with clinical state (Elzinga et al. 2011; Bus et al. 2011; Gass and Hellweg 2010; Sartorius et al. 2009). Nevertheless, the regulation of the BDNF levels in hippocampus, serum, and whole blood in FSL and FRL rats adds to the hypothesis that neurotrophic factors may be related to the pathophysiology of depression.

Similar to findings with BDNF, we have recently characterized vascular endothelial growth factor (VEGF) in the FSL rats. VEGF protein, but not mRNA, expression in the hippocampus and frontal cortex were found to be significantly decreased in the FSL compared with FRL rats, while no differences were found in the striatum, hypothalamus or serum (Elfving et al. 2010b).

Neurogenesis and Cell Proliferation

Hippocampal neurogenesis has been implicated in the etiology of depression and has been suggested to constitute the final common mechanism underlying antidepressant treatments (Santarelli et al. 2003). In order to further explore the hypothesis that reduction in hippocampal neurogenesis contributes to the etiology of depression, which was essentially based on studies on healthy rats exposed to repeated or chronic stressors, the FSL model was tested under a variety of circumstances (Petersen et al. 2008, 2009; Husum et al. 2006; Bjornebekk et al. 2007).

We found that adult FSL rats have significantly more BrdU-immunoreactive (IR) cells in the dentate gyrus compared with FRL, and aging caused an exacerbated loss of these cell types in the FSL. FSL animals treated chronically with nortriptyline, there was no apparent effect on the number of BrdU-IR cells, although it significantly decreased the immobility time in the FST (Petersen et al. 2009). Taken together, these results clearly demonstrate a dissociation of the effects of antidepressants on behavior in the FST and cell proliferation. Thus SSRIs and tricyclics can decrease immobility in the FST without affecting the cytogenesis and, conversely, increased cytogenesis is not necessarily reflected in decreased depression-like behavior in FST. These data are of importance since they indicate that changes in cell proliferation may be sufficient, but are not necessary for antidepressant effects of currently used antidepressants in the FSL/FRL model.

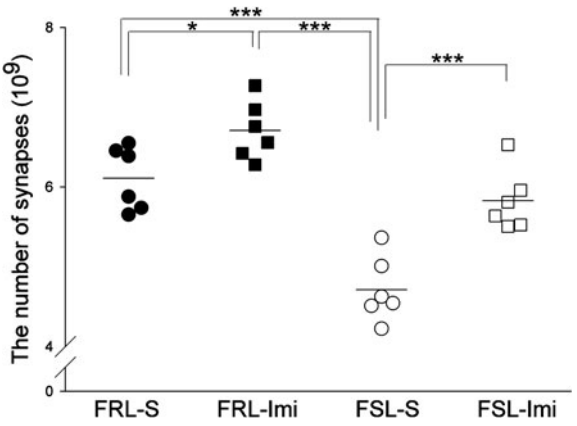

Fig. 3 Effect of Imipramine on the non-perforated spine synapses in FSL and FRL rats. The total number of spine synapses in the CA1 stratum radiatum was significantly smaller in the FSL rats compared to the FRL rats. Following 3 weeks of Imipramine (Imi, 15 mg/kg/day) there were a significant increase in the spine synapses in both FSL and FRL, thereby normalizing the FSL spine synapse numbers. (* $p < 0.05$; *** $p < 0.001$). Modified from (Chen et al. 2010) with permission. © John Wiley & Sons

Also other aspects of brain remodeling have been proposed to be essential for development of disease. Thus, both the hippocampal volume (Videbech and Ravnkilde 2004) and synaptic morphology may play a role (Nestler et al. 2002). Therefore, we have investigated changes in hippocampal volume, neuron and synapse numbers in the FSL and FRL following chronic imipramine therapy, using design-based stereological methods (Chen et al. 2010). We found that the volume and the number of neurons and synapses were significantly smaller in the FSL saline group compared with the FRL saline group, a feature which was reversed following imipramine treatment (Fig. 3). Our experiments illustrate the importance of using a disease model to study cell proliferation and effects of treatments that could potentially be translated to human condition.

Cardiovascular and Metabolic Function

Depression is a well-known risk factor for the development of ischemic heart disease and is associated with increased cardiovascular morbidity and mortality (Barefoot and Schroll 1996; Egede et al. 2005; Hemingway and Marmot 1999; Rugulies 2002). Major depression doubles the risk of adverse cardiovascular events within 12 months in patients with newly diagnosed coronary heart disease (Carney et al. 1988) and increases the risk of mortality after acute myocardial infarction (Frasure-Smith et al. 1993). The presence of diabetes has been found to double the risk of co-morbid depression (Anderson et al. 2001), and a meta-analysis has shown that depression increases the risk of developing type 2 diabetes

in adults by 37% (Knol et al. 2006). In a study comparing the myocardial responsiveness to ischemia/reperfusion injury and the effects of ischemic preconditioning in hearts from FSL rats using SD rats as controls, it was observed that the myocardial infarct size was significantly larger in the FSL rats than in the SD rats following ischemia/reperfusion injury, but have maintained cardioprotective mechanism following ischemic preconditioning (Solskov et al. 2010). In the same study, it was also demonstrated that FSL were hyperinsulinemic, with a strong tendency in different levels of fasting glucose levels compared with SD rats (Solskov et al. 2010).

However, in a recent study performed in Aarhus, we have not been able to detect any difference in fasting glucose levels in FSL compared with FRL (Abildgaard et al. 2010). Metabolic stress induced by a high fat diet increased insulin levels during an oral glucose tolerance test in both FSL and FRL, with fasting blood glucose levels significantly increased by high fat diet in the FSL rat (Abildgaard et al. 2010). Interestingly, the metabolic changes were associated with increased depression-like behavior in the FST and cognitive impairments in the object recognition test in the FSL only. These findings confirm the FSL as a model with a greater metabolic susceptibility, and further highlight the usefulness of the model in translational interdisciplinary depression research.

2.1.2 Gene × Environment Interactions

Interactions with the environment, which can have negative or positive consequences, have also been found to be a major determinant of disease. For example, psychosocial stress in adulthood impairs the health condition of the individual (Lupien et al. 2009; Bale et al. 2010; Reber et al. 2007), whereas social support or exercise exert beneficial effects on somatic and mental health (Brene et al. 2007; Dishman et al. 2006; Dunn and Dishman 1991; Young 1979; Neumann 2009).

The consequences of acute, subchronic or chronic stress are largely dependent on the individual (and genetically determined) stress susceptibility, and there is good evidence that FSL and FRL as well as HAB and LAB rats provide good models to study gene × environment interactions. For example, as mentioned above, a subchronic adult stress paradigm significantly upregulates the NO signaling pathway in the FSL only (Wegener et al. 2010), and metabolic stress more severely impacts the FSL compared with the FRL (Abildgaard et al. 2010). In another series of experiments, we compared adult female FSL and SD rats in a paradigm of 7 weeks of social isolation at the age of 29 weeks, and observed increased number of BrdU-IR cells in the FSL, whereas it had no impact in the SD strain (Bjornebekk et al. 2007). Other environmental stimuli may be experienced positive. Thus, we have examined the effect of physical activity using running wheels. We observed that voluntary wheel running had antidepressant effects and selectively altered NPY and NPY Y1 receptor and opiate expression in the FSL, but not FRL, rats further supporting a role of NPY in their phenotype

(Bjornebekk et al. 2006, 2010). These findings parallel and support the results from human studies (Russo-Neustadt et al. 1999; Ransford 1982).

In addition to adult stress exposure, gene × environment interactions have been described with respect to early-life stress, either prenatally or postnatally. Thus, a large number of human and animal studies show a strong association between an adverse fetal or immediate postnatal environment and behavioral and emotional development later in life (Abe et al. 2007; Maccari et al. 2003; Nagano et al. 2008; O'Connor et al. 2002; Tazumi et al. 2005; Van Den Bergh et al. 2005). Stressful experiences during early life have been hypothesized to enhance susceptibility (eventually triggered by adult stress) for mental illness (Cottrell and Seckl 2009; Fumagalli et al. 2007; Maynard et al. 2001).

Prenatal stress studies have not yet been carried out in FSL/FRL. However, the classical post-natal stress paradigm, maternal separation, in FSL and FRL have been demonstrated to exacerbate the depression-like behavior of the FSL, but not the FRL (El Khoury et al. 2006). Treatment with escitalopram selectively decreased depression-like behavior in the FST in both maternally non-separated and separated FSL, but not FRL rats (El Khoury et al. 2006). Maternal separation in FSL has been also been found to reduce NPY in dorsal hippocampus of both female and male FSL rats compared with FRL rats (Jimenez-Vasquez et al. 2001; Wortwein et al. 2006).

In another study, we analyzed hippocampal synaptic transmission and plasticity in vivo and ionotropic receptors for glutamate in FSL and FRL rats subjected to maternal separation. A strong inhibition of long-term potentiation (LTP) and lower synaptic expression of NR1 subunit of the NMDA receptor were found in FSL rats (Ryan et al. 2009), and unexpectedly maternal separation induced a remodeling of synaptic plasticity only in FSL rats, reducing inhibition of LTP accompanied by marked increase of synaptic NR1 subunit and GluR2/3 subunits of AMPA receptors (Ryan et al. 2009). This finding is in line with the demonstration that maternal separation increased the hippocampal cell number, while consistently with this increase, chronic escitalopram treatment reduced the cell number (Petersen et al. 2008; Husum et al. 2008).

In a study of basal differences in synaptic signaling between FSL and FRL rats, as well as on consequences of maternal separation in adulthood, it was found that the FSL rats showed basal differences in the interaction/activation of distinct synaptic mediators purified hippocampal synaptosomes (Musazzi et al. 2010). In addition, following maternal separation, the FSL rats displayed a blunted response of the mediators, suggesting a synaptic dysfunction in the FSL animals (Musazzi et al. 2010). Escitalopram treatment restored some but not all alterations observed in FSL rats after early-life stress, suggesting that early gene-environment interaction may cause life-long synaptic changes affecting the course of depression-like behavior and response to drugs (Musazzi et al. 2010).

Finally, using an open-ended approach based on a proteomic analysis of serum, maternal separation was found to induce changes in inflammation and transport proteins in FSL rats (Carboni et al. 2010), changes that were partly reversed

following treatment with escitalopram or nortriptyline (Carboni et al. 2010). No comparison between early-life stress in FSL and FRL was carried out.

These experiments underline that the consequences of environmental factors are strongly determined by the genetic background, suggesting that a genetically shaped phenotype can be further modulated by environmental factors.

2.1.3 Response to Treatment

A detailed review of the different studies, where the FSL rat has been used to test for the antidepressant-like effects of drugs lies beyond the scope of this text, and only a brief overview is given in the Table 3. A detailed review of the classical antidepressants and selective serotonin reuptake inhibitors (SSRIs) as well as a variety of novel agents that presumably have different actions from the well-characterized antidepressants, can be found elsewhere (Overstreet 2002, 2005).

2.2 Learned Helplessness Rats (cLH/cNLH)

The learned helplessness (LH) paradigm is a well characterized rat model of depression, in which the animals are exposed to uncontrollable and unpredictable aversive events, i.e., foot shock (Overmier and Seligman 1967). The model has good face and predictive validity, including alterations in HPA axis activity and REM sleep characteristic of depression (Maier 1991; Breier et al. 1987; Henn and Vollmayr 2005). However, in outbred rats not the entire proportion of animals become helpless. Therefore, breeding of helpless lines from Harlan SD outbred rats was initiated in 1990 to achieve a higher yield of helpless animals following inescapable shock-training (Vollmayr and Henn 2001; Henn and Vollmayr 2005). This resulted in congenitally learned helpless (cLH) rats exhibiting a helpless phenotype without exposure to uncontrollable shock, and a congenitally not learned helpless (cNLH) strain being resistant to the effects of inescapable shock (Vollmayr and Henn 2001).

2.3 Fawn Hooded Rats

A high degree of comorbidity between alcoholism and depression have been reported (Merikangas and Gelernter 1990; Cloninger et al. 1979). The Fawn-Hooded (FH/Wjd) rat is an inbred strain of rat, originally selected from a background of platelet serotonin storage abnormality (Tschopp and Zucker 1972). The rat has been reported to exhibit both high immobility in the FST, elevated serum corticosterone and high voluntary ethanol intake, measures that have been linked

with depression and alcoholism in humans (Rezvani et al. 2002, 2007). For example, the FH/Wjd rat drinks up to 6 g/kg 10% ethanol per day, and responds to drugs that are effective in humans with a reduction in alcohol intake (Rezvani et al. 1999). Interestingly, the exaggerated immobility in the FST and the hypercorticosterone levels can be also attenuated following chronic antidepressant treatments (Aulakh et al. 1988, 1993; Rezvani et al. 1999). The FH/Wjd also exhibits abnormalities in the central serotonergic function (Aulakh et al. 1994; Bendotti and Samanin 1987; Arora et al. 1983; Dumbrille-Ross and Tang 1981), but whether these serotonergic abnormalities contribute to both behaviors remains to be determined. In addition, the first results showing decreased NPY in hippocampus in a model of depression were obtained in the FH, changes that were reversed following ECS (Mathe et al. 1998). These findings were of great heuristic value as they led to subsequent identification of reduced NPY expression in other, both genetic and environmental models, including the FSL/FRL as described above.

2.4 Wistar-Kyoto Rats

The Wistar-Kyoto (WKY) rat strain was developed as the normotensive control strain for the spontaneously hypertensive rat, and bred from the Wistar strain starting in 1963 (Okamoto and Aoki 1963). The WKY presents with hormonal, behavioral, and physiological measures that mimic those found in depressed patients, such as increased immobility in the FST (Lahmame et al. 1997; Rittenhouse et al. 2002; Paré 1992, 1994) and dysregulation of the HPA and hypothalamic–pituitary–thyroid axes (Solberg et al. 2001; Redei et al. 1994; Gómez et al. 1996). However, the WKY responds with variable degree to antidepressants (López-Rubalcava and Lucki 2000; Lahmanie and Armario 1996; Lahmame et al. 1997), and has therefore been proposed as a model of treatment-resistant depression (Lahmame et al. 1997). Therefore, the model has been further developed into 'WKY most immobile' (WMI) and 'WKY least immobile' (WLI) rats (Will et al. 2003).

2.5 Swim Low-Active/Swim High-Active Rats

Since low motor activity and a condition of passive stress coping in a swim test have been proposed to represent depression-like behavior in the rat, SD rats were bred in accordance with the motor-activities starting in 1987 (Weiss et al. 1998). Two rat lines have been obtained, Swim Low-Active (SwLo) and Swim High-Active (SwHi) rats, which differ dramatically in FST behavior. The SwLo rats show little struggling and much floating, while SwHi rats show the reverse (Weiss et al. 1998). Importantly, when SwLo rats were given antidepressant, chronic but

not acute administration increased swim-test activity of SwLo rats (West and Weiss 1998a). Information on neurotransmitter involvement was limited, but studies suggest involvement of both glutamatergic (Tabb et al. 2007) and dopaminergic (West et al. 1999a, 1999b) mechanisms as well as alterations of the stress axis (Gutman et al. 2008).

2.6 High/Low Stress Reactivity Mice

As mentioned before, dysfunctions (hyper- or hypo-activity) of the HPA axis may play a prominent role in the development of major depressive disorders (De Kloet et al. 1998; Holsboer 2000; Bale 2006). Therefore, attempts of generating animal models mimicking these neuroendocrine core symptoms have been made in order to unravel parameters underlying increased or decreased stress reactivity (Touma et al. 2008). Mice expressing a hyper- or a hypo-reactivity of the HPA axis were selected for the 'high reactivity' (HR) and the 'low reactivity' (LR) breeding line. Compared with LR animals, the HR males and females were 'hyperactive' in some behavioral paradigms (Touma et al. 2008), resembling symptoms of restlessness and agitation often seen in melancholic depression. On the neuroendocrine level, the circadian rhythm of glucocorticoid secretion revealed a flattened diurnal rhythm (Touma et al. 2008), mimicking findings from patients suffering from melancholic depression (Deuschle et al. 1997; Keller et al. 2006).

3 Selectively Bred Models on Anxiety

3.1 Rats Selectively HAB and LAB Anxiety-Related Behavior

An adequate level of innate anxiety and fear is essential for survival of individuals and species. Naturally, there exists a wide individual range in trait anxiety: from extremely low to extremely high. Similarly, in humans, anxiety-related pathologies including generalized anxiety, panic disorders or social phobia, reflect extremes in trait anxiety with significant contributions of adverse life events shaping the individual anxiety phenotype. In order to reveal neuroendocrine, neurochemical and neurogenetic mechanisms of a complex behavioral phenotypes such as anxiety, and in order to identify potential targets for psychotherapy, we have established and extensively studied selectively bred HAB and LAB rats (Landgraf and Wigger 2002; Landgraf et al. 2007; Neumann et al. 2010). This approach is particularly promising to further our understanding of genetic mechanisms underlying anxiety-related disorders. Other relevant rodent models for anxiety-related behavior include exposure to early-life stress (Wigger and

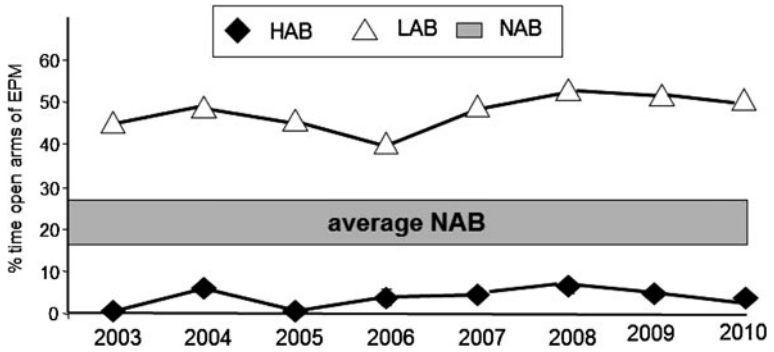

Fig. 4 Anxiety-related behavior of male and female HAB, LAB and non-selected NAB rats on the elevated plus-maze (EPM) which is consistent over the years between 2003 and 2010

Neumann 1999; Huot et al. 2001), chronic stress in adulthood (Barrot et al. 2005; Reber et al. 2007; 2008), or transgenic modifications (Bale 2006; Mantella et al. 2003). Recently, the Landgraf group succeeded in establishing also mice lines selectively bred for high (M-HAB) and low (M-LAB) anxiety-related behavior (see Table 1; Landgraf et al. 2007).

Since 1993, we have selectively and bi-directionally bred outbred Wistar rats for high (HAB) versus low (LAB) anxiety-related behavior based on their behavioral performance on the EPM at the Max Planck Institute of Psychiatry in Munich and, since 2002, at the University of Regensburg (Landgraf and Wigger 2002; Landgraf et al. 2007; Neumann et al. 2010; see Fig. 4). Male and female HAB and LAB rats are selected at the age of 9 weeks for further breeding only, if the percentage of time spent on the open arms of the elevated plus maze (EPM) is below 5% and above 40–45%, respectively. For experimental purposes, HAB rats with an anxiety level of less than 10% and LAB rats with more than 35% time on the open arms during testing at the age of 9 weeks are used.

3.1.1 Key Features of the HAB/LAB Model

Anxiety-Related Behavior

The behavioral profile of HAB and LAB rats with respect to the selection criteria has been reliable and robust over the last 10–15 years (Liebsch et al. 1998b; Neumann et al. 2010; see Fig. 4), is present over all seasons, independent of sex or age and could be confirmed in different European laboratories. The extremes in anxiety could be confirmed in a battery of relevant behavioral tests, including the EPM, the open field, the light dark box and the holeboard (Slattery and Neumann

2010; Ohl et al. 2001; Henniger et al. 2000). In addition, HAB rats are unable to properly extinguish inappropriate fear in tests for conditioned anxiety despite similar acquisition of fear (Muigg et al. 2008). Thus, although bred for high innate non-conditioned anxiety on the EPM, this finding reveals that HAB rats also display exaggerated responses to conditioned fear, which makes them a potentially useful model for posttraumatic stress disorder. Also, LAB rats were able to extinguish this fear faster than non-selected Wistar rats (NAB), again showing robust trait differences between these lines.

Effects of Anxiolytic Treatment

The predictive validity of the HAB/LAB model is substantial, and anxiolytic agents reverse or attenuate the high anxiety phenotype seen in HAB rats.

Acute treatment with the reference anxiolytic drug, diazepam (1 mg/kg, i.p), reduced anxiety in HAB rats on the EPM or in the light–dark box, whereas it was without effect in LAB rats (Liebsch et al. 1998a; Jochum et al. 2007). In addition to its effects on anxiety-related behavior in HAB rats, diazepam also corrected the abnormal pain sensitivity seen in HAB rats (Jochum et al. 2007). Similar to diazepam, we have repeatedly found a reliable and profound anxiolytic effect of chlordiazepoxide (20 mg/kg, i.p.) with relatively low individual differences in responsiveness (Slattery; Beiderbeck and Neumann, unpublished).

Also, manipulation of various relevant anxiogenic and anxiolytic neuropeptide systems of the brain, such as arginine vasopressin, CRH, oxytocin and neuropeptide S, respectively, was found to be effective in reducing the high level of anxiety seen in HAB rats.

Depression-Like Behavior

Importantly, mimicking the high degree of comorbidity of anxiety and depression mentioned above, HAB rats are also characterized by depression-related behavior in the FST, independent of sex (Keck et al. 2003b; Slattery and Neumann 2010; Frank and Landgraf 2008).

Effects of Antidepressant Treatment

Chronic treatment with antidepressant drugs reduces the depression-like status in HAB rats. Treatment of male HAB rats with the SSRI paroxetine during a period of 8 weeks markedly increased active stress coping in the FST to a level similar to that seen in LAB rats. The reversal of the depression-like phenotype was accompanied by a reduction of the high level of hypothalamic vasopressin expression and normalization of the Dexamethasone-suppression/CRH-challenge test (DEX/CRH test) described below (Keck et al. 2003a). However, paroxetine did not alter vasopressin expression or any anxiety-related behavior assessed in LABs, underlining the impact of the genetic predisposition to trait anxiety and comorbid depression-like behavior on drug effects.

Recently, landmark studies have shown that inactivation of Brodmann Area 25 (BA25) using deep brain stimulation alleviated depressive symptoms in severely depressed patients (Mayberg et al. 2005). Interestingly, transient pharmacological inactivation using muscimol of the infralimbic cortex, the rodent correlate of BA25, decreased the high inborn depression-like behavior of the HAB rats supporting their face and predictive validity for affective disorders (Slattery et al. 2010). It remains to be determined whether this region may also be involved in their innate anxiety phenotype.

Several lines of evidence resulting from both preclinical and clinical studies support the view that repetitive transcranial magnetic stimulation (rTMS) of left frontal brain regions exerts antidepressant effects (Post and Keck 2001). Thus, acute, subchronic or long-term rTMS sessions reduced the duration of immobility in rodents in the Porsolt swim test, exert neuroprotective effects both in vitro and in vivo and change the expression of BDNF and cholecystokinin similar to those reported after antidepressant drug treatment (Post and Keck 2001). To test for rTMS efficacy in a psychopathological rat model, HAB and LAB rats received stimuli over two 3-day series (Keck et al. 2001a). The stimulation point was set at the left frontal cortex in order to mimic clinical conditions. Repetitive transcranial magnetic stimulation increased active stress coping in HAB rats, rendering these animals indistinguishable from LAB rats. The rTMS-induced shift in HAB animals towards active stress coping was markedly higher than has previously been reported in "normal" Wistar rats (Zyss et al. 1997). Furthermore, rTMS treatment resulted in a significant attenuation of the neuroendocrine hyper-response of the HPA axis to and acute ethologically relevant stressors characteristic for HAB rats, whereas their high anxiety level remained unchanged.

Cognition

Emotionality and cognition are closely inter-related, as the assessment of environmental stimuli, in particular of potentially dangerous situations, is dependent on the acquisition and storage of information. To further test this hypothesis, the cognitive performance of HAB and LAB rats has been estimated on the modified holeboard, where HABs showed a clearly improved declarative memory performance indicating a better learning strategy despite (or because of) a more passive performance during the test (Ohl et al. 2002). No differences in working memory in a visual-spatial task were found (Ohl et al. 2002).

In confirmation, line-dependent differences were also seen with respect to social memory and cognition abilities, as HAB, but not LAB, males could distinguish between a known and an unknown juvenile after a 30-min inter-exposure interval (Landgraf and Wigger 2002). The lack of social preference seen in LABs (Lukas and Neumann, unpublished) may underlie their impaired social memory.

To which extent the high central vasopressinergic drive (Wigger et al. 2004; Bosch et al. 2006; Bosch and Neumann 2010) contributes to the improved learning and memory performance in HAB rats, remains to be shown. Brain vasopressin is

an important neuromodulator promoting cognitive functions (Engelmann et al. 1996) and may thus facilitate the storage of adverse emotional situations and shape future stress coping.

Social Behaviors

Other behavioral differences, which have been established over the years of selective breeding for high versus low trait anxiety, include a variety of social behaviors (Neumann et al. 2010), which is of interest as several psychopathologies often are accompanied by various abnormalities in social interactions including aggression, social phobia, or impaired social bonding.

Inter-Male Aggression

Male HAB and LAB rats differ in inter-male aggression with LAB males showing an extreme high level of offensive behavior in the resident-intruder test (Veenema et al. 2007), a finding which is also reflected by an abnormal aggression of LAB males displayed towards females and anesthetized males compared with NAB rats (Neumann et al. 2010). In contrast, HAB males rather display an intermediate level of intermale aggression (Beiderbeck et al. 2007; Neumann et al. 2010; Veenema et al. 2007). Thus, the selective breeding for low trait anxiety resulted in a socio-behavioral phenotype characterized not only by low anxiety and fear responses, reduced risk assessment and an active stress coping style, but also by abnormal social behaviors in different social settings, thus providing an excellent model for studying mechanisms of pathological aggression.

Social Phobia

In a relevant behavioral setup for social phobia/social preference, NAB and HAB rats show social preference. In this test, rats are allowed to explore a small wired cage placed into the cage of the experimental rat. Social preference is seen, when the animal explores the small cage longer and more often, when it contains a conspecific animal. Here, LABs, in general, do not search for social contact, display reduced contact to cage mates (Ohl et al. 2001) and do not show social reference, which can also be interpreted as social phobia (Lukas and Neumann, unpublished).

Maternal Care

Line-differences in social behavior are also found in females with respect to maternal care and maternal defense behavior (maternal aggression). Here, HAB dams are more protective towards their pups, leave the nest less often, show more arched back nursing and more maternal aggression (Bosch et al. 2005; Bosch and Neumann 2010; Neumann et al. 2005a). A significant contribution of high activity of the brain vasopressin system seen in HAB dams to their maternal behavior profile could recently be identified (Bosch and Neumann 2008, 2010). Interestingly, a correlation between high maternal trait anxiety and the intensity of

maternal care has also been found in mouse dams bred for high and low anxiety and, again, line-dependent differences in brain vasopressin appear to underlie the behavioral differences (Kessler et al. 2011).

Pain

Similar to depressed patients, HAB rats have been shown to exhibit decreased sensitivity to thermal pain (Jochum et al. 2007). Acute administration of diazepam partly reversed the abnormal pain response. Also, treatment of male HAB rats with the SSRI citalopram, daily for 8 weeks, reduced anxiety-related behavior as assessed on the EPM and reversed the abnormal thermal pain response in HAB rats (Jochum et al. 2007). As, in contrast to the thermal pain sensitivity, the sensitivity to visceral pain has been found to be elevated in patients suffering from affective disorders (Haug et al. 2004), it would be of interest to test visceral pain threshold in HAB versus LAB rats.

Sleep

In depressed patients, sleep disturbances are a common symptom, as mentioned above. Analysis of sleep patterns in HAB and LAB rats revealed similar circadian fluctuation in sleep-wake behavior, but differences in their spontaneous sleep–wake behavior. HAB rats spend less time awake and more time in non-REM sleep (Lancel et al. 2002). This difference is particularly pronounced during darkness and this is in accord with the observed decreased locomotor activity of HAB rats during the nighttime (Liebsch et al. 1998b). The larger amount of non-REM sleep in the HAB group was not associated with an increased length of non-REM episodes, but with a greater number of sleep episodes, suggesting a higher non-REM sleep fragmentation. HAB rats also displayed less pre-REM sleep and REM sleep than LAB rats during the light period. Thus, the sleep pattern of HAB rats seems to be opposite to that found in depression, and further studies are needed.

Hypothalamic-Pituitary Adrenal Axis

The behavioral differences between HAB and LAB rats are accompanied by distinct neuroendocrine underpinnings. Although basal levels of plasma ACTH or corticosterone reflecting basal activity of the HPA axis do not differ, the responsiveness of the HPA axis to a mild emotional (and non-social) stressor is more pronounced in HAB compared with LAB males (and with non-selected Wistar rats; Landgraf et al. 1999; Neumann et al. 2010), thus resembling psychiatric patients (Holsboer 2000). However, the neuroendocrine response to social stimuli is aggravated in LABs, paralleling their abnormal social behavioral responses described above (Neumann et al. 2010; Veenema et al. 2007). HAB rats also show

an aberrant hormonal secretion pattern during the DEX/CRH test (Keck et al. 2002; Neumann et al. 2010), a clinical test used for the neuroendocrine characterization of depressed patients (Ising et al. 2005). Intravenous administration of DEX revealed DEX-non-suppression and, thus, impairment of negative feedback regulation in HAB rats. Subsequent administration of CRH resulted in pronounced ACTH and corticosterone responses, which are absent in LAB and NAB rats. This indicates a contribution of endogenous vasopressin, which—together with exogenous CRH—triggered pituitary secretion of ACTH despite (impaired) DEX-suppression. Consequently, and in support of this hypothesis, an acute intravenous administration of a vasopressin V1a receptor antagonist abolished the ACTH and corticosterone hyper-response and normalized the DEX/CRH test outcome in HAB rats, pointing towards a significant contribution of the endogenous brain vasopressin system in these neuroendocrine abnormalities (Keck et al. 2002). Furthermore, chronic administration of paroxetine over 8 weeks prevented the abnormal DEX/CRH response in HAB rats with a concomitant attenuation of the vasopressin hyperdrive in the hypothalamic paraventricular nucleus (PVN, Keck et al. 2003b).

Neuronal Activity

In addition to neuroendocrine responsiveness, neuronal responses within brain regions belonging to the anxiety/fear circuitry to anxiogenic, social or pharmacological stimuli also differ between HAB and LAB rats (Muigg et al. 2007; Salchner et al. 2006; Salome et al. 2004; Frank et al. 2006). For example, in response to airjet stimulation, an escape-provoking stimulus, HAB rats show a higher neuronal activity in various hypothalamic areas including the medial preoptic and anterior hypothalamic areas, and in the nucleus accumbens as estimated by quantification of the expression of the early immediate gene *fos* (Salome et al. 2004). Similarly, in response to forced swimming, neuronal responses within selected cortical, septal, and hypothalamic areas were more pronounced in HAB males. These neuronal responses could be attenuated after chronic paroxetine treatment (Muigg et al. 2007), which could underlie the reduction in depression-like behavior seen after antidepressive treatment in HAB rats.

Neuropeptides

Vasopressin

Given the importance of brain vasopressin in the regulation of anxiety, depression, and neuroendocrine stress coping (Landgraf and Neumann 2004; Frank and Landgraf 2008), the vasopressin gene was considered a candidate gene in high trait anxiety. Indeed, high vasopressin mRNA expression within the parvocellular part of the PVN both under basal conditions and in response to stressor exposure is a reproducible characteristics for male and female HAB rats (Keck et al. 2003b;

Wigger et al. 2004; Bosch et al. 2006; Bosch and Neumann 2010; Frank and Landgraf 2008). Consequently, increased vasopressin immunoreactivity and local neuropeptide release were both found in the HAB hypothalamus. In addition, vasopressin V1a receptor binding is also elevated within the lateral septum of HAB rats, a region relevant for the regulation of anxiety and social behaviors (Keck et al. 2003b).

In line with our hypothesis of a substantial contribution of high endogenous vasopressin activity to the high anxiety and depression-like phenotype of HAB rats, blockade of vasopressin V1a receptors within the hypothalamic PVN reduced their anxiety level and resulted in a more active coping style (Wigger et al. 2004). Further, the V1a antagonist (i.v.) normalized the pathological outcome of the DEX/CRH test in male HABs (Keck et al. 2002). These findings, reflecting both construct and predictive validity, confirm the involvement of endogenous central vasopressin in the behavioral and neuroendocrine phenomena of high trait anxiety and depression.

Interestingly, line-dependent differences in brain vasopressin also appear to contribute to differences in social behavior, i.e. intermale aggression as well as maternal behavior (Beiderbeck et al. 2007; Veenema et al. 2007; Bosch et al. 2010; Bosch and Neumann 2008).

Given the robust increase in brain vasopressin activity in HAB rats in parallel to their anxiogenic and hyperresponsive neuroendocrine phenotypes, underlying genetic mechanisms are likely. Indeed, 10 single nucleotide polymorphisms (SNPs) within the vasopressin promoter were found between the lines. In addition, a single base pair substitution has been identified in the first intron of the vasopressin gene of HAB rats itself (Murgatroyd et al. 2004). One of the SNPs identified was found to be embedded in a potential transcription factor binding site (CArG box), the locus of binding to the transcriptional repressor CBF-A. Functional relevance of the SNP was identified by in vitro DNA binding assay and revealed that CBF-A binding to the CArG box derived from the HAB allele was indeed diminished, resulting in an attenuated transcriptional repression of the vasopressin gene. Thus, this genetic mechanism may underlie vasopressin over-expression in the PVN of HAB rats (Murgatroyd et al. 2004; Landgraf et al. 2007). Interestingly, out of 100 outbred Wistar rats, the HAB allele was found in 3 rats (heterozygeous) indicating a gene frequency of 1.5% in the general Wistar rat population.

In addition to vasopressin, other brain neuropeptides such as CRH, oxytocin, prolactin, NPY, or neuropeptide S are important neuromodulators of emotionality, in particular of anxiety- and depression-related behaviors. Thus, an endophenotype of high or low anxiety accompanied by differences in active or passive stress coping style is likely to be accompanied by differences in the activity of several endogenous neuropeptide and other neurotransmitter systems.

Corticotropin-Releasing Hormone

Corticotropin-Releasing Hormone (CRH) exerts anxiogenic and depression-like effects, and CRH mRNA expression has recently been found to be up-regulated within the PVN of HAB rats compared with LAB rats (Bosch et al. 2006). In contrast,

line-dependent differences in CRH receptor binding could not be identified. Thus, differences in endogenous CRH system activity are likely to contribute to the emotional phenotype of HAB rats, as suggested in depressed patients (Nemeroff 2004; Keck and Holsboer 2001). Indeed, acute peripheral administration of the non-peptide CRH 1 receptor antagonist R121919 reduced anxiety levels on the EPM in HAB, but not LAB, rats and reduced stress-induced corticotropin secretion in both rat lines (Keck et al. 2001b).

A high level of anxiety could also be due to an attenuation of endogenous anxiolytic neuropeptides such as oxytocin (Neumann et al. 2000; Waldherr and Neumann 2007), prolactin (Torner et al. 2001; Donner et al. 2007) and/or neuropeptide S (NPS; Xu et al. 2004).

Oxytocin

Besides its capacity to modulate complex social behaviors, oxytocin is an established anxiolytic neuropeptide of the brain (Blume et al. 2008; Neumann 2008) and has antidepressive properties (Slattery and Neumann 2010). However, differences in central oxytocin expression or release were not found between HAB and LAB rats, except in lactation (Bosch et al. 2007).

In order to study potential anxiolytic or antidepressive effects of oxytocin in a psychopathological animal model, HAB and LAB rats were treated i.c.v. with either oxytocin or an oxytocin receptor antagonist (Slattery and Neumann 2010), which was only effective in female but not male rats: chronic oxytocin reduced the high anxiety level of HAB females on the EPM, whereas chronic i.c.v. treatment with the oxytocin antagonist increased anxiety only in female LAB rats without any effect in HABs or males. In contrast, acute manipulation of the oxytocin system did not alter anxiety-related behavior independent of sex and trait anxiety. Also, passive/active stress coping in the FST was not altered by any manipulation of the oxytocin system. Thus, chronic oxytocin seems to be a promising therapeutic strategy in particular for the treatment of anxiety disorders in women.

Prolactin

Prolactin has distinct anxiolytic properties, and the brain prolactin is involved in the regulation of anxiety and stress coping (Torner et al. 2004; Bunck et al. 2009; Ditzen et al. 2010). Plasma prolactin levels were found elevated in HAB rats in response to a mild emotional stressor (Neumann et al. 1998; Landgraf et al. 1999). The behavioral significance of this finding needs to be studied, as plasma prolactin does not reflect intracerebral prolactin release patterns (Torner et al. 2004), but peripheral prolactin can cross the blood brain barrier. However, differences in brain prolactin expression, release or receptor binding have not been studied in HAB and LAB rats until now.

Neuropeptide S

Neuropeptide S (NPS) is another powerful anxiolytic neuropeptide (Xu et al. 2004; Leonard et al. 2008; Vitale et al. 2008), and our preliminary results indicate substantial genetic and activity differences of the endogenous brain NPS system between HAB

and LAB rats. For example, the latter express more NPS receptors in the hypothalamus (Slattery, Wegener, Naik, Mathé, Neumann, unpublished). In order to confirm the anxiolytic properties described in non-selected male mice (Xu et al. 2004) and rats (Vitale et al. 2008) in a psychopathological animal model, we acutely treated HAB and LAB rats with i.c.v. NPS 45 min prior to EPM testing can (Slattery et al. 2008). Indeed, preliminary evidence suggest that NPS reversed the high trait anxiety of HABs and exerted modest antidepressant effects (Slattery et al. 2008). Further, i.c.v. NPS improves consolidation of extinguished learned fear (Sartori et al. 2009).

Other Neurochemical Differences

Serotonin Disturbances in serotonergic neurotransmission are likely to contribute to the pathophysiology of anxiety and depression disorders and to underlie the hyperactivity of the HPA axis (Holsboer 2000). In HAB rats, serotonin 1A receptor expression was found to be reduced in the hippocampus, whereas the expression of the serotonin transporter binding sites was increased. Further, the basal availability of extracellular serotonin as estimated in microdialysates did not differ between the lines, but serotonin release in response to emotional stress was abolished in HAB rats. Chronic paroxetine markedly increased the stress-induced rise in hippocampal serotonin release, but did not alter receptor expression (Keck et al. 2005). Thus, the reduced raphe-hippocampal serotonergic transmission of HAB rats, which is evident both at the presynaptic (release) and postsynaptic (receptor) level, are likely to contribute to their high emotionality.

Hippocampal Neurogenesis

Consistent with the generally elevated stress responsiveness including HPA axis hyperreactivity and impaired negative feedback functions, we found reduced hippocampal cell survival and neurogenesis in 43-days old male HAB rats (Lucassen et al. 2009). Specifically, the number of newly generated surviving (BrdU-positive) cells in the subgranular cell layer/subgranular zone of the hippocampal dentate gyrus was found to be lower in HAB versus LAB rats. Further, the number of hippocampal doublecortin-positive cells reflecting neurogenesis is lower in HAB rats (Lucassen et al. 2009).

These results show that the high level of anxiety and activity of the HPA axis may affect cell survival in HAB rats, which may, in turn, also be partly responsible for their behavioral phenotype.

3.1.2 Gene × Environment Interactions

Early life stress, such as prenatal and immediately postnatal stress is a well-characterized risk factor for the development of affective disorders in adulthood,

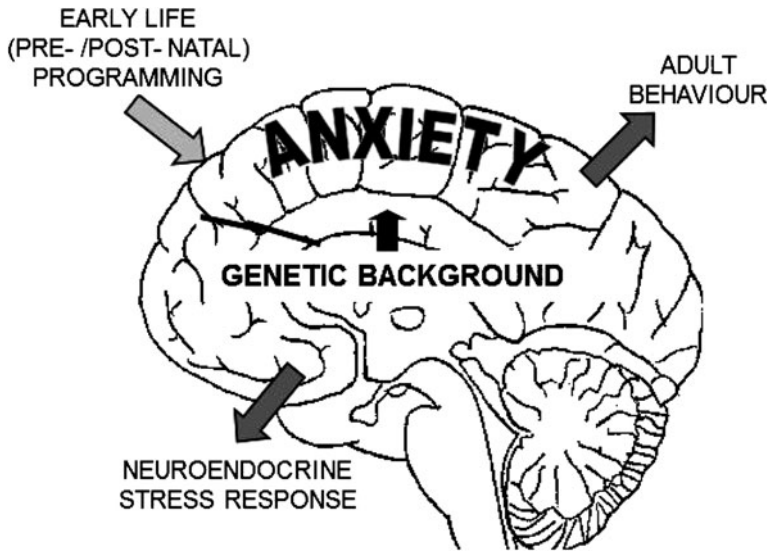

Fig. 5 Gene × early environment interactions shape adult behavioral and neuroendocrine stress responses as seen in rats with genetic determination of trait anxiety

and there are well documented interactions of genetic and environmental factors (Caspi et al. 2003; Fig. 5, see also Sect. 2.1.2). Selectively bred rodents with clear genetic determinants are valuable models for studying gene × environment interactions. Both prenatal stress as well as postnatal maternal separation resulted in line-dependent behavioral effects seen in adult HAB and LAB rats.

Gene × prenatal environment interactions: Surprisingly, after exposure to prenatal stress between pregnancy days 4 and 18 (exposure of the pregnant dam to maternal defeat by an unknown lactating resident daily for 45 min between pregnancy days 4 and 10, and to restraint between pregnancy days 11 and 18 for 60 min daily) adult male HAB rats became less anxious (see Fig. 6). This was confirmed in two independent tests for anxiety-related behavior, i.e. the EPM and the modified holeboard (Bosch et al. 2006). The opposite behavioral consequences of prenatal stress were accompanied by opposing effects on central vasopressin and CRH mRNA expression: whereas the genetically determined high level of hypothalamic vasopressin mRNA expression of HAB rats was not altered by prenatal stress, it was elevated in early life stressed LAB male offspring (Fig. 6). Similarly, the genetic difference in CRH expression within the PVN with high levels in unstressed HAB compared with LAB controls was also at least partly abolished by prenatal stress. Further, after prenatal stress the high HPA axis response to a mild stressor found in HAB rats was reduced and found to be indistinguishable from unstressed and prenatally stressed LABs (Bosch et al. 2006).

Opposing effects of prenatal stress were also found with respect to hippocampal neurogenesis, which has been shown to be stress-sensitive and implicated in depression (Pittenger and Duman 2008). As mentioned above, the survival of

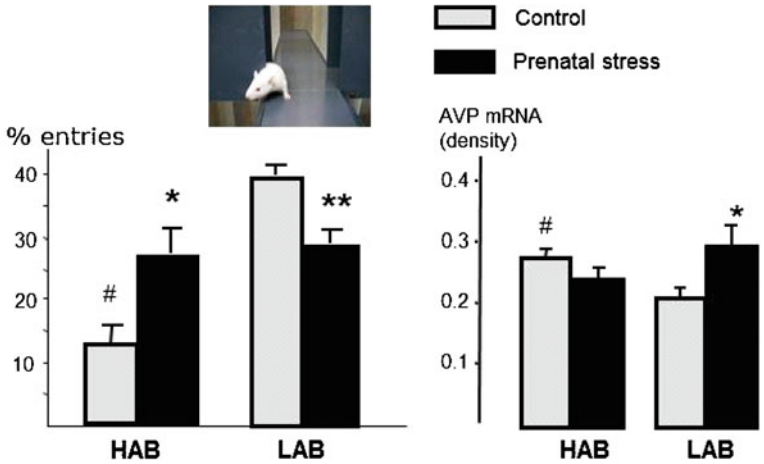

Fig. 6 Opposite effects of prenatal stress on anxiety-related behavior on the EPM (% entries open arms; left) and basal vasopressin mRNA expression in the hypothalamic PVN (right) in male HAB and LAB adult offspring indicating gene × early environment interactions. # versus LAB; * versus respective control. Adapted from (Bosch et al. 2006)

newly generated hippocampal cells is lower in young unstressed HAB compared with LAB males (day 43 of life). Interestingly, while prenatal stress caused a further reduction in the number of BrdU and doublecortin positive cells in the subgranular zone of the hippocampal dentate gyrus in HAB rats, it did not affect this parameter in the LAB rats (Lucassen et al. 2009). Although detailed mechanisms underlying the opposing effects of prenatal stress in HAB and LAB rats are unknown, line-dependent differences in the activity of the placental enzyme 11-beta hydroxysteroid dehydrogenase type 2, which catalyzes maternal corticosterone to inert 11-dehydrocorticosterone are likely to contribute (Lucassen et al. 2009).

Gene × postnatal environment interactions: Opposite effects on emotionality and neuroendocrine responsiveness and, consequently, approximation of the HAB and LAB behavioral and neuroendocrine phenotypes were also found after immediate postnatal stress, i.e. after maternal separation (Fig. 7). Daily 3-h separation of HAB and LAB offspring from the mother between postnatal days 2 and 15 reduced anxiety in adult HABs as seen on the modified holeboard, but rather increased (EPM) or had no effect (holeboard) in LABs (Neumann et al. 2005b). Further, the HPA axis hyper-responses seen in HAB control rats became attenuated after postnatal stress, whereas maternal separation did not significantly alter neuroendocrine responses in LAB rats (Neumann et al. 2005b; Fig. 7).

These experiments underline that the consequences of environmental factors are strongly determined by the genetic background. Vice versa, even a robust genetically determined individual behavioral phenotype can be shaped by environmental factors; likely via epigenetic mechanisms (Murgatroyd et al. 2009).

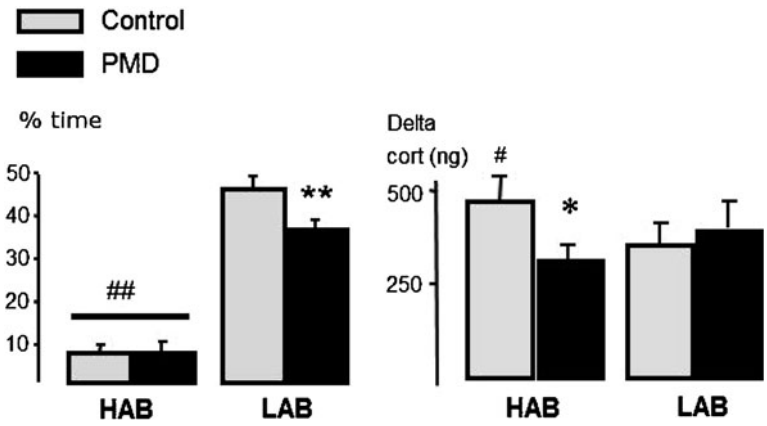

Fig. 7 Opposite effects of postnatal stress (periodic maternal separation; PMD) on anxiety-related behavior on the EPM (% time open arms; left) and plasma corticosterone response to novel environment exposure (elevated platform, right) in HAB and LAB adult offspring indicating gene × early environment interactions. # versus LAB; * versus respective control. Adapted from (Neumann et al. 2005b)

The mitigating effect of early life experiences on behavioral and neuroendocrine parameters in rats representing extremes in trait anxiety may also reflect an evolutionary benefit, as the genetic variability among individuals of a species is sustained, while maintaining adequate responses to potentially dangerous stimuli in adulthood. Our results in HAB and LAB rats after pre- and postnatal stress exposure further indicate that gene × environment interactions can be found at behavioral, neuroendocrine, neuronal and gene levels indicating their complexity.

3.2 HAB LAB Mice

Although various selectively bred rat lines are useful tools for studying behavioral and especially neuroendocrine parameters of depression and anxiety, as well as environmental factors shaping innate stress coping style, genetic studies such as the functional analysis of candidate genes underlying, for example, high trait anxiety or depression-related behavior, are a priori limited in rats. Therefore, Landgraf and co-workers also generated mice selectively bred for high (M-HAB) versus low (M-LAB) anxiety-related behavior (Kromer et al. 2005). After 9 generations of continuous breeding (sibling mating), a robust behavioral divergence had been achieved. High trait anxiety has been confirmed on the EPM and in the light–dark box; further, M-HAB mice pups show more ultrasound vocalization, which was reversed by diazepam (Kromer et al. 2005). In agreement to what has been found in HAB and LAB rats, M-LAB mice are more active in several tests for depression-like behavior (FST, tail suspension). Also, as seen in HAB and LAB

rats, differences in the hypothalamic expression of vasopressin are likely to underlie their trait anxiety and also line-dependent social behavior (Kessler et al. 2011), but here M-LABs show signs of central diabetes insipidus, i.e. low vasopressin expression and availability compared with M-HAB and non-selected CD1 mice (Kessler et al. 2007). A SNP in exon 1 of the vasopressin gene of LAB mice causes an amino acid substitution in the signal peptide of the vasopressin precursor, and is likely to impair processing and trafficking of the precursor (Bunck et al. 2009; Kessler et al. 2007). Besides vasopressin, differences in the expression of the cytosolic enzyme glyoxalase-I, which is of potential interest in the context of various psychopathologies, have been found in these mice (Kromer et al. 2005; Hambsch et al. 2010). Thus, selectively bred mice have a high potential to reveal novel candidate genes underlying high trait anxiety.

3.3 Floripa H and L Rats

The Floripa H and L rat lines, have been developed based on selection for high and low locomotion in the central aversive area of an open field, an experimental measure of fearfulness in rodents (Ramos and Mormede 1998). The Floripa H and L lines differ from each other not only for the selected behavior, but also for other experimental indices of anxiety, such as the approach towards the open arms of the elevated plus maze and the white compartment of the black/white box (Ramos et al. 2003). In addition, compared with Floripa L, the Floripa H rats show less depression-like behavior in the FST (Hinojosa et al. 2006), suggesting the Floripa rats to be a combined model of both anxiety and depression. The Floripa L female rats consumed more ethanol than their Floripa H counterparts at concentrations of 6 and 10% in a two-bottle choice protocol (Izídio and Ramos 2007), however the connection to the anxiety-like phenotype remains to be determined.

3.4 Maudsley Reactive and Nonreactive Rats

Based on reactivity in the open field, with defecation and urination being the central variables, two lines of rats, later termed the Maudsley high reactive (high defecation, MHR) and low, nonreactive (low defecation, MLR) rats, were bred from Wistar in the 1950s aiming to model the human personality dimension of emotionality (Broadhurst 1957, 1960, 1962, 1975). The overall conclusion of the several studies published were that Maudsley reactive rats yielded higher scores in several tests of anxiety-like/avoidance behavior than non-reactive animals (Blizard and Adams 2002). Although this approach was useful to study individual differences in anxiety-like/avoidance behavior, it has not been pursued intensively in recent years (Pawlak et al. 2008; Blizard and Adams 2002).

3.5 High/Low Avoidance Rats: RHA/RLA; SHA/Bru and SLA/Bru

Several rat breeding lines have been selected for learning to actively avoid foot shocks in a two-way shuttle-box. The Roman high avoidance (RHA) and Roman low avoidance (RLA) Wistar rats (Bignami 1965), the Long–Evans rats (Brush et al. 1979, 1985, 1989; Brush 2003), and Syracuse high and low avoidance rats (SHA/Bru and SLA/Bru) are the most prominent examples. Although these attempts differ in nature, some of the common characteristics include differences in learning and memory, and a number of emotion-related behavioral and neuroendocrine characteristics. A detailed review can be found in (Brush 2003).

4 Conclusions

In conclusion, the existing data on selectively bred rodent models, in particular of the FSL/FRL and HAB/LAB rats reviewed above, reveal the importance of rodent breeding lines for studying neurobiological, neuroendocrine and genetic mechanisms underlying anxiety- and depression-related diseases. Essentially, the development of potentially novel therapeutic strategies targeting brain neuropeptide systems such as NPY, vasopressin, CRH, oxytocin or neuropeptide S will be enabled and promoted using such relevant and complementary animal models. Moreover, selectively bred rat and mouse lines provide an important tool in order to provide further evidence for gene × environment interactions demonstrating differential vulnerabilities, for example to prenatal or immediate postnatal adverse life events. The combination of genetic models with various stress paradigms is likely to mimic the human situation more accurately.

Given their behavioral and neuroendocrine phenotype, the neurobiological mechanisms underlying their anxiety- and depression-related behavior, as well as successful pharmacological attempts to reverse the psychopathological phenotype, the FSL/FRL and HAB/LAB rats fulfill the requirements of face, construct and predictive validity of an animal model. Therefore, they should be further exploited to discover potential novel therapeutic strategies.

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