Animal Models of Depression Vulnerability

Jaanus Harro

Abstract The rapid increase in the number of proposed animal models of depression reflects the dissatisfaction with our current state of knowledge on neurobiology of depression and unsuccessful drug development. Results obtained with even the best validated models can be difficult to compare. Because evidence from epidemiological studies suggests that depression occurs in biologically predisposed subjects under the impact of adverse life events, increasing attempts have been made to use the diathesis–stress concept in animal models. In this way, factors underpinning vulnerability to depression have been identified by measuring behavioural traits analogous to facets of human personality, or created by inducing neurochemical lesions. Stressful interventions administered prenatally, in early life or in adulthood have been combined with other vulnerability factors including genetic changes. As a result, several putative animal models of endophenotypes of depression or depression vulnerability have been proposed. Diathesis–stress models may aid in separating adaptive and maladaptive strategies in coping with stress, and understanding the relevant neurobiology. Studies comparing effects of stress on males and females should reveal to which extent the pathogenetic processes leading to depression can be specific to sex/gender.

Keywords Depression · Animal models · Predisposition · Resilience · Diathesis–stress · Endophenotypic · Acute and chronic stress · Maternal separation · Inter-individual variability

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1 Introduction

In recent years, animal models of human psychopathology have been continuously growing in number, and this is particularly true for animal models of depression. Such a trend probably reflects a variety of developments in neuroscience, but one of these, pertinent to the present chapter, is the increased understanding that realistic and translational animal models of depression must incorporate the notion that not all people develop clinical depression even if being genetically similar or living at equally harsh conditions (Anisman et al. 2008). Furthermore, as one of the important aims of animal models is to aid in screening for novel drugs active as antidepressants, the limited success of recent psychotropic drug development is suggesting that there may be something wrong with the conventional approach. It would be unfair to lay all blame on insufficient animal models, as many other key shortfalls are evident in the process (Williams 2011). Nevertheless, rethinking the way, we consider the functions of animal models and their development, appears due.

While many available models are sensitive to existing antidepressants, few new leads have made it to the clinic, and many false positives have been reported. Indeed, if the drugs with antidepressant properties require large numbers of patients to be treated to detect efficacy compared to placebo, how can experiments based on small groups of laboratory animals, provided in distinct batches from a variety of breeding companies and uniformly treated, consistently yield such amazing efficacy of the known drugs? It appears likely that animal models are highly optimised for detecting the effect of the established antidepressants, and consequently the models often lead us to findings that are not at the core of the

neurobiology of depression but somehow collateral to it. This may have been at least implicitly perceived by depression researchers who are increasingly looking for novel models or modifications that often are laboratory specific, hampering meaningful comparison of the data.

Regarding the often-used animal models of depression and antidepressant screening tests, there are many comprehensive reviews available that describe the mainstream models; these also describe several less well-characterised models and discuss conceptual issues and methodological caveats (e.g., Cryan et al. 2002; Cryan and Mombereau 2004; Cryan and Slattery 2007; El Yacoubi and Vaugeois 2007; Holmes 2003; Jacobson and Cryan 2007; Kalueff et al. 2007; McArthur and Borsini 2006; Nestler et al. 2002; O'Neill and Moore 2003; Refojo and Deussing 2012; Renoir et al. 2012; Samuels et al. 2011; Willner 1990, 1997). Several of these reviews also systematically address the issues of construct, face and predictive validity of animal models, as laid out by McKinney and Bunney (1969), Willner (1990), and Geyer and Markou (1995). Despite the fact that validity concerns always receive much attention, there is often disagreement between the authors on how best to model depression. The reasons for this can be found in the above cited papers. The present chapter is not aimed to provide another review of the well-known models or attempt to rectify the many controversies in the current literature. Instead, it is dedicated to some important conceptual issues revolving around the concept of depression vulnerability, and to views on the best approaches to model it.

2 What is Vulnerability to Depression?

Oxford Dictionary (2011) defines "vulnerability" as follows: "exposed to the possibility of being attacked or harmed, either physically or emotionally." The origin of the word has been traced to early seventeenth century, and comes from late Latin *vulnerabilis*, derived from *vulnerare* 'to wound,' and from *vulnus* 'wound.' According to the collective wisdom of Wikipedia (2011), vulnerability refers to the inability to withstand the effects of a hostile environment. Vulnerability is not thought of as a persistent state: a window of vulnerability is a time frame within which defensive measures are reduced, compromised or lacking. Hence, we ought to consider the harmful factors that reduce our capabilities to resist or compensate for the impact of such factors that can lead to depression. Factors causing vulnerability to depression and the clinical condition can be extracted from the epidemiological studies. It has to be acknowledged that individuals affected by depression display a wide variation in clinical symptoms and signs, and the diagnostic conventions are consensus driven, and thus to some extent arbitrary (Fava and Kendler 2000). Nevertheless, the large numbers of epidemiological studies in this area provide the most reliable starting point.

Epidemiological studies suggest that predisposing factors with a probable causal link to depression include sex/gender, stressful life events, adverse

childhood experiences and certain personality traits (Fava and Kendler 2000). Of the latter, the best evidence is for neuroticism, a stable personality trait that reflects the predisposition to develop emotional upset under stress (Eysenck 1951). Many medical conditions can lead to clinical depression, and there are cases of depression inducing drugs as was recognised many years ago for the monoamine depleting alkaloid reserpine (Drevets and Furey 2009). Genetic factors contribute to the overall risk of depression, but also influence the sensitivity of individuals to the pathogenetic effects of environmental adversity (Kendler et al. 1995).

Altogether, this evidence suggests that the pathogenetic process of depression proceeds stepwise, building on blocks of previously emerged predisposition, and alterations brought about by adverse environment. How this could happen in terms of neurobiology has been elaborated on (e.g., Harro and Oreland 2001), but is mostly beyond the scope of this chapter. For the development of depression vulnerability models, the evidence that depression has both environmental and genetic origins provides a guide to approaches that are based on enhanced vulnerability of some animals as compared to other, more resilient counterparts.

3 How Do We Define Animal Models of Depression Vulnerability?

The first explicit attempt to define animal models of depression vulnerability, and to compare the validity of such models, was made 10 years ago. For this analysis, Willner and Mitchell (2002) suggested that some animal models introduced as models of depression should rather be considered models of vulnerability to depression. These authors defined models of depression vulnerability as models that "increase the ease with which an analogue of major depression may be evoked, or a presentation analogous to dysthymia (chronic mild depression)." According to the vulnerability approach, animals in the models of depressive diathesis would either express "depressive" features even in the absence of stress (corresponding to the DSM-IV condition of dysthymia or minor depression) or appear no different from their non-vulnerable counterparts if there is no manipulation present to precipitate depression. The authors went further by listing 11 animal models of vulnerability to depression, and assessed these models for their predictive, face and construct validity. The authors classified these models into genetic, genomic, developmental and lesion models; the models were congenital learned helplessness, Flinders Sensitive Line (FSL) rats (muscarinic hypersensitivity), Roman High Avoidance rats, Fawn Hooded rats, hypothalamus-pituitary-adrenal axis (HPA) transgenic mice, 5-HT transporter knockout mice, corticotropin-releasing factor (CRF) receptor subtype knockout mice, tachykinin receptor knockout mice, neonatal antidepressant treatment, prenatal/neonatal stress and olfactory bulbectomy.

Many readers might consider most of these models as models of depression per se, without thinking in terms of whether they might represent models of depression

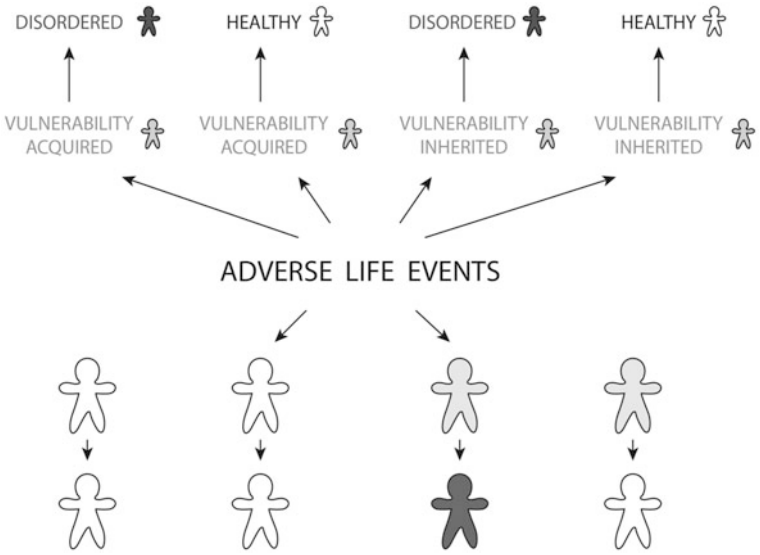

Fig. 1 *The diathesis–stress concept* Depression develops under strain brought about by adverse life events in those individuals who have respective predisposition. Such a predisposition can be either inherited or acquired during lifetime, and does not cause the disorder even not in all subjects who are subject to lifetime adversities owing to protective factors that for psychiatric disorders remain poorly defined

vulnerability. Indeed, it would be difficult to distinguish models of depression and depression vulnerability on the basis of assumptions on aspects of validity. This introduction of the vulnerability concept is, nevertheless, most valuable as it puts the focus on the salience of environmental factors in the pathogenesis of depression, and thus on the controllable aspects of construct validity of the models. In the following sections the approach to vulnerability models will be top down, departing from the known etiopathogenetic factors of depression that have guided us to the diathesis–stress concept.

4 The Diathesis–Stress Concept

The diathesis–stress or vulnerability–stress model of psychopathology has been used to explain behaviour as a result of two types of impact. A diathesis, or vulnerability, is a predispositional factor, or set of factors, that makes possible a disordered mental state (Ingram and Luxton 2005). The source of the disposition can be defined more or less broadly, and it could be either genetic or developmental, but it ought to be explainable in biological terms, and possess a relatively permanent, enduring trait. The stress from life experiences, superimposed on pre-existent biological differences conferring the vulnerability, will then be

capable of eliciting psychopathology that would not be brought about in those individuals free of the predisposition.

It can be argued that vulnerabilities can be modifiable, and they probably are as the biological traits depend on the organisation of the brain that is meta stable rather than fixed. For model building the pragmatic approach would still keep vulnerability as the stable predispositional measure, and treat changeable states as the consequences of life events. It is then the stressful life event or series of events that challenges the homeostasis that has been established in the vulnerable brain, and shakes the state of the nervous activity so that the next meta stable state could, with higher probability, be the substrate of a condition diagnosed as a psychiatric disorder (Fig. 1). This is, however, not to say that the strength of the diathesis would never change: it is conceivable that at some points during life, relatively less stress is necessary to tip the balance (Ingram and Luxton 2005). The difficulty of uncovering "genes for depression" makes it likely that vulnerability has several components. Furthermore, while the concept suggests that the shift from the vulnerability stage to the disorder stage is qualitative, the processes that underlie the predisposition state can be balanced in more ways than just one.

How exactly stressful life events cause the switching from vulnerability to disorder is unclear. It is conceivable that greater exposure to life's adversities is pathogenetic, and it is also possible that some predispositions lead individuals to choose lifestyles that expose them to adverse life events that are either more serious or occur with higher probability. On the other hand, it has also been proposed that patients with depression have not encountered more severe life events, and it is their reactions that are exaggerated (Richardson 1991).

At this point, it has to be recalled that stressful life events, adverse childhood experiences and personality traits like neuroticism are not specifically associated with major depression, nor are there any gene products known to specifically cause depression. But neither is any symptom of affective disorders pathognomonic or even highly specific. Nevertheless, while the current diagnostic system has made psychiatric comorbidities rather a rule than an exception, each affected individual eventually is in a certain clinical state that must be the end product of the interaction of predisposition and environmental adversities. Thus, with the available knowledge, joint analysis of the effects of known risk factors will be helpful in disentangling the web of psychiatric nosology into more self-standing units. We cannot expect a greater level of understanding from the animal models in terms of symptoms, endophenotypes, biomarkers, aetiology or pathogenesis than that achieved from our level of understanding of the clinical pathology.

5 How Do We Learn Whether Vulnerability Is Truly Vulnerability?

One of the fundamental problems with modelling behavioural disorders has been the attempt to simulate changes in behaviour without really knowing the causes of the deviations (McArthur and Borsini 2006). Using simple unspecific behaviours of rodents as endpoints to measure human symptoms have led to endless discussions on, for example, what does immobility in the forced swimming test measure? This author believes that behaviours displayed in the forced swimming test can reliably measure a number of different psychological states depending upon the specific characteristics of the task and the neurobiological state of the animal (strain). Moreover, we can only find out the most likely construct for each well-defined condition by a laborious validation procedure (Harro 2004). Similarly, reduction in sucrose intake can probably reflect other psychological dimensions than just anhedonia, especially if it is recorded in food and water deprived animals.

An objective measure of vulnerability in an animal model should be congruent with a measure of human vulnerability to depression. This is very difficult to achieve for behavioural endpoints in rodents, because the adaptive value of simple behaviours in conditions highly artificial for the species remains a matter of interpretation. This, indeed, has allowed depression modelling to accept counter-intuitive approaches, as in the case of the olfactory bulbectomy model that displays a reliable behavioural readout in terms of hyperactivity in an open field. Nevertheless, this hyperactivity that hardly helps to meet the face validity requirement for a depression model is sensitive to a range of antidepressants, and the model is characterised by a number of neurobiological deviations reminiscent of depression (Song and Leonard 2005).

There appears to be two major approaches to increase our understanding of what we measure when taking behavioural readouts. First, to focus on ethologically relevant and situation-specific measures that reflect with high probability affective neurobiological states of the animal (Panksepp 1998). Second, to apply the diathesis–stress concept-derived models and pay special attention to behaviours that emerge under stress in vulnerable individuals. Subsequently, in either case, higher priority should be given to endophenotypic changes that can be directly translated to and from the pathogenesis of clinical depression.

The neurobiological vulnerability concept was introduced to the interpretation of animal models by Anisman and Zacharko (1990), who suggested that factors that "favor the provocation of amine depletions," or that diminish the intrinsic capacity of the nervous system to adapt to such depletions, increase vulnerability to depression. Monoamine-related measures still appear as legitimate targets, while a number of other candidate measures have been discovered. Since much work is going on to identify biomarkers of psychiatric conditions in humans, this approach should also yield the detection of vulnerability markers. Then, future research should aim at the development of animal models that display similar markers. As such objective markers of vulnerability are not yet available, the

safest way forward appears to be to rely on the etiopathogenetic principle, that is, applying stress on animals with a biological background thought of as depression related.

6 A Note on Genetic Models and the Diathesis–Stress Concept

As this volume contains a chapter on genetic models of depression (see chapter by Barkus), these are not discussed in detail in the present chapter, but it should be mentioned that several advances have been recently made in using the diathesis–stress approach with vulnerable mouse strains. Indeed, some strains of mice have behavioural and physiological features that suggest construct and face validity as a model of depression, and some such models have been found to provide predictive validity. While many mouse models are used without including adverse life events, life events take place for the laboratory animals notwithstanding the experimental design, and the vulnerability factor could play a role even if there is formally no stress applied. Naturally, this is relevant not only for genetically modified mice but also for any animal stock with presumed predisposition to depression-like pathogenetic process. In addition to the minor life events that are inevitably happening in the animal house, vulnerability may be producing psychopathology via other routes such as internal, physical deviations building up stress from inside as well as behavioural tendencies that make the animals play a role in creating their own stresses, for example, by engaging in aggressive encounters with cage mates (Ingram and Luxton 2005; Harro 2010). However, each strain will establish over a few generations adaptive strategies to maintain homeostasis, such that the behaviours displayed by the vulnerable strains could indicate different coping styles rather than anything congruent with human clinical symptoms.

There is a large body of the literature on affect-related differences between rodent strains, and these data are not always easy to reconcile. For example, while C57BL/6 mice are considered the resilient strain in comparison with BALB/c mice, they have been used as a stress susceptibility strain in comparison with DBA/2 mice (Ventura et al. 2002). A recent review by Jacobson and Cryan (2007) compiled a large amount of information on the behavioural features of different mouse strains, and pointed out a number of complicating factors. However, one conclusion that emerges from analyses of models of anxiety, depression and antidepressant sensitivity is that the BALB/c strain has a reproducible predisposition to negative affect (Belzung and Griebel 2001; Jacobson and Cryan 2007). This is confirmed by the diathesis–stress approach: BALB/c mice were compared to C57BL/6 with regard to responsivity to chronic mild stress, and it was found that stress reduced learning specifically in the BALB/c mice (Palumbo et al. 2009). Interestingly, a differential alteration in levels of neuronal nitric oxide synthase (NOS) isoforms was also observed. NOS activity has been previously implicated in neurobiology of depression and may be attenuated during 5-HT hypofunction (Harvey et al. 2006).

Maternal separation has recently been reported to decrease the genetic expression of histone deacetylase in neocortex in adult BALB/c mice, an alteration that was not observed in C57BL/6 mice (Levine et al. 2012). These data suggest that epigenetic programming may be differentially recruited in mouse strains with different affective behaviour. Several genetically modified mice with suspected vulnerability to depression have also been submitted to chronic stress regimens. Examples include cannabinoid receptor $CB_1^{-/-}$ mice (Aso et al. 2011), vesicular glutamate transporter $vGLUT1^{+/-}$ mice (Garcia–Garcia et al. 2009), mice with impaired glucocorticoid receptor expression (GR-i mice) and 5-HT transporter $^{-/-}$ mice (Lanfumey et al. 2000). Importantly, all these studies have been supportive of the diathesis–stress concept, with the stress vulnerability of the genetically manipulated mice being greater than wild-type controls.

7 Adverse Early Life Events

A range of adversities in childhood including physical and sexual abuse, poor parent–child relationships and parental discord and divorce, almost certainly increase the risk for depression later in life (Fava and Kendler 2000). In animal studies, early life stress paradigms have utilised various manipulations, in particular handling, maternal separation, social deprivation and enriched versus impoverished environments. The validity of these paradigms as models of depression has been considered limited but in theory the programming effects elicited by the manipulations should, indeed, confer vulnerability rather than disease (Schmidt et al. 2011). Thus, early life stress paradigms could be very useful as part of the diathesis–stress approach.

Early life stress studies have revealed major changes in neuroplasticity and learning in adulthood that depends on environmental adversities. For example, in rats the adult male offspring of less caring mothers had reduced synaptic plasticity in stress-free conditions, but enhanced synaptic plasticity in stressful conditions (Champagne et al. 2008). These differences in neuroplasticity were mirrored in performance in learning tasks. Similar findings were obtained when rats were submitted to the presumably more stressful maternal separation paradigm; for example, while neurogenesis was reduced by severe early life stress and spatial learning was impaired, long-term potentiation was greater and fear conditioning was enhanced (Oomen et al. 2010). It is tempting to speculate that such neurobiological alterations underlie the selective attention to negative stimuli and rumination on dysfunctional thoughts in the development of depression.

7.1 Maternal Separation

Several animal models are based on the notion that disruption of the mother-infant bond is an important risk factor for disorders of affect. How the adult will emotionally respond depends on the quality of early environment, and this association appears to be mediated by early influences of the parents on brain development. The most robust approach to disrupt the mother-infant bond is daily separation of mothers from their offspring, and this has been an increasingly applied technique to mimic early life adversities brought about by inadequate maternal care. In monkey infants initial protests and the subsequent despair-like state induced by separation from their mothers was an early depression model in primates (McKinney and Bunney 1969), and the model can be applied in a variety of other species (e.g., Panksepp et al. 1978; Francis et al. 1999).

Probably, the most carefully studied model so far in the diathesis–stress approach is the FSL rat (originally bred for increased responses to an anticholinesterase drug) that exhibits several depression-like features when compared to the Flinders Resistant Line (FRL) (Overstreet et al. 2005). In FRL rats exposure to early life stress in the form of maternal separation did not reduce significantly the swimming behaviour in the modified Porsolt's test, but further reduced swimming in the vulnerability model, FSL rats (El Khoury et al. 2006). Whereas escitalopram was ineffective in FRL rats, the antidepressant brought swimming behaviour of maternally separated FSL rats to control levels (El Khoury et al. 2006). Swimming was recorded as the sum of all active behaviours in these experiments. In further studies, the stress resilience of the FRL rat was, however, less clear-cut. In one experiment, maternal separation increased immobility in both lines (non-
significantly in FSL, but this could have been related to a ceiling effect), and the efficacy of escitalopram was notable in naïve FSL but much less potent in maternally separated FSL (Musazzi et al. 2010). In another experiment, maternal separation had no statistically significant effect on immobility, but a strong trend toward an increase was observed in both strains (Piubelli et al. 2011). Interestingly, in this experiment escitalopram was not effective in the maternally separated rats. Nevertheless, escitalopram attenuated the upregulation of hippocampal NMDA receptor subunit 1 immunoreactivity, which is an alteration observed selectively in FSL rats after maternal separation (Ryan et al. 2009). Further studies should reveal reliable endpoints in this diathesis–stress model, and whether these endpoints have relevance to clinical depression.

7.2 Prenatal Stress

An increasing number of prospective studies have revealed that if a mother has been under stress while pregnant, her child is substantially more likely to have

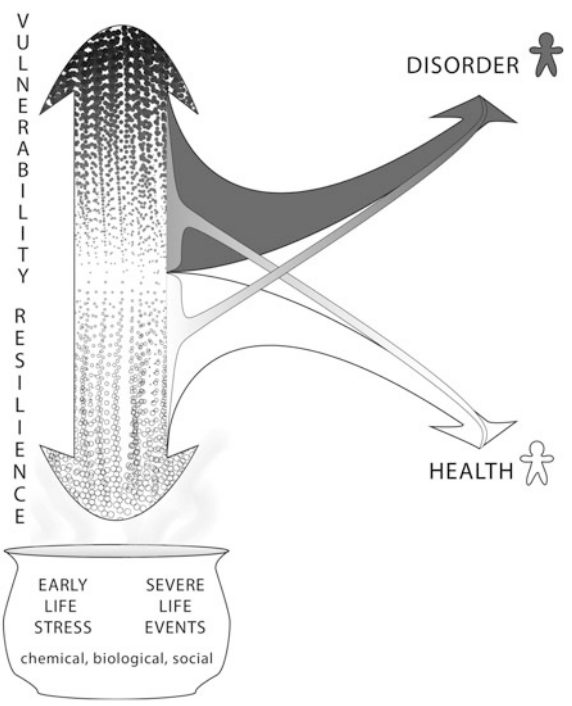

Fig. 2 *Dimensionality of the diathesis–stress concept* Both vulnerability and resilience to depression are probably quantitative in nature, and do not represent a single dimension. While the probability to respond to the variety of lifetime adversities with depression is increased by diathesis and reduced by resilience, mechanisms appear to exist that mediate an increase in resistance in subjects who would be considered as predisposed to the disorder

emotional or cognitive problems, independently of maternal postnatal affective state (Talge et al. 2007). Prenatal environment can have long lasting consequences that track into adulthood. For example, in animal studies, repeated exposure to severe stress during the second half of pregnancy increased anxiety and vulnerability to addictive drugs and led to a phase advance in the circadian rhythm and increased in corticosterone secretion and paradoxical sleep in adulthood of the offspring (Maccari et al. 2003). Thus, prenatal stress applied to animals with depression vulnerability represents a promising research strategy.

8 Stressful Life Events During Adulthood

Many environmental adversities, such as job loss, marital difficulties, major health problems and loss of close personal relationships, are linked with a substantial increase in risk for the onset of depression (Fava and Kendler 2000). In animal modelling, comparisons between studies can also be very approximate, for instance, because of the many types and schedules of stress applied. A simple classification can separate acute stress from chronic, chronic stress with a single stressor (often restraint, Rosecrans and De Feo 1965) from chronic variable stress (Katz et al. 1981; Willner et al. 1992) and perhaps chronic social stress from non-

social stressors. It should be noted that the same type of stressor could serve as both the source of environmental adversity and signal of induced vulnerability, dependent on the paradigm; for example, early life stress applied to animals genetically predisposed to depression would serve as a stressor, while maternally separated animals can be further exposed to stress as adults, with the expectation that vulnerability had been acquired during the early life adversity.

One such an attempt, however, revealed that while maternal separation elicited exaggerated HPA axis responses, chronic variable stress in adulthood did not further increase but instead decreased HPA activity as well as CRF expression in the amygdala (Ladd et al. 2005). This finding leads to reconsideration of the functional value of stress-related alterations in the CNS (Fig. 2). Further studies have demonstrated that maternal separation followed by social defeat in adulthood can lead to heightened expression of the 5-HT transporter and tryptophan hydroxylase in the dorsal raphe nucleus (Gardner et al. 2009a, b), findings interpreted along the lines of the diathesis–stress concept. Social defeat stress may be a more severe but ethologically relevant stressor compared to chronic variable stress and less manageable by the built-up resilience, a notion that receives support from oxidative metabolism mapping (Harro et al. 2011). Studies that apply stress early in life may still benefit from the neuro-constructivist approach that emphasises the natural gradual process of ontogenetic development (Karmiloff-Smith 2006), leaving space for different adaptive strategies to adversities.

8.1 Acute Stress

While the opinion prevails that humans suffer from depression mostly after chronic stress, a single episode of stress can also precipitate depression, but it must be very intense or interpreted as such. When using a behavioural measure as the readout in the diathesis–stress model, it is preferable to select an independent test not related to performance during stress. For example, if the acute stressor is forced swimming, then immobility during stress may not be a reliable indicator. While we have little insight into the animal's subjective experiences of the severity of stress, it appears safer to make use of chronic stress paradigms. Humans are more likely to be subjected to periods of mild intermittent or prolonged stresses (McArthur and Borsini 2006), and behavioural alterations after such impacts seem less likely to reflect positively adaptive shifts than reactions to acute insults. Methodologically, it is also worth considering that the time course of the stress response to an acute stressor is an additional source of variation in comparisons across different stressors and laboratory conditions. For studies of chronic stress it is to be safer to assume a stabilised stress response than for an acute challenge. Nevertheless, additional adaptive changes to the stress response can occur at later stages (Matrov et al. 2011).

A few interesting studies have, however, attempted to precipitate a depression-like state in vulnerable animals by applying an acute but severe stressful stimulus.

Roman low- and high-avoidance (RLA/RHA) rat strains were bred for different performance in avoidance tasks. While the parameter for selection was learning, the segregating trait might rather be anxiety since the RLA-rats appear as more anxious (Broadhurst and Bignami 1965; Brush 2003). However, whilst a single 1-h session of social defeat elicited depression-like behaviour lasting for up to 10 days, it did not differentiate between the lines (Meerlo et al. 1997). Nevertheless, social stress may not be the optimal stressor for the RHA/RLA paradigm, as the anxiety tests that differentiate between the lines do not include a social interaction test but rather anxiety tests based on exploration of the environment. Furthermore, the strains differ at baseline regarding sensitivity to rewards (see Harro 2010).

In the case of the olfactory bulbectomy rat, arguably one of the more reliable models for detecting antidepressant drugs, animals were compared with regard to their acoustic startle reflex and shock-induced sensitisation of the startle reflex (McNish and Davis 1997). It was found that while bulbectomised animals were normal at baseline, they displayed a pronounced increase in responding during conditioning, and developed sensitisation of the startle reflex at shock intensities that did not produce sensitisation in control animals. This evidence supports the notion that olfactory bulbectomy leads to enhanced vulnerability to stressors.

The diathesis–stress approach has been applied with stressors for which it is not obvious whether they are (sub)chronic or acute, since the stressed state can last for days even though stress exposure time is relatively short. In the case of the FSL/FRL model, rats were submitted to 5 days of swimming stress of which four sessions were escapable but the final, fifth session inescapable (Wegener et al. 2010). Animals were sacrificed 2 h after the last session, at which point increased hippocampal constitutive NOS activity and neuronal NOS levels were found only in the FSL rats. Thus, no production was increased in hippocampus of the vulnerable strain. Since NOS activity has been implicated in neurobiology of depression and may be attenuated during 5-HT hypofunction (Harvey et al. 2006), this study suggests one of the possible pathways that could explain the diathesis–stress mechanism.

Withdrawal from addictive drugs, especially psychostimulants, can induce a number of behavioural symptoms reminiscent of depression, and a variety of associated neurochemical changes in monoaminergic and other transmitter systems (Renoir et al. 2012). Depression can also occur after serious somatic disease, and especially after challenges to the immune system (Anisman and Merali 2003). In the Fawn-Hooded rat model of depression (Rezvani et al. 2002), responses to interleukin were found to be distinct from the Sprague–Dawley rat (Simmons and Broderick 2005). Thus, these stressors also offer interesting possibilities to examine the neurobiology of predisposition to depression.

8.2 Chronic Stress

Long-term intermittent distress caused by adverse life events, either single or repeated, is an important contributor to the development of depression. In animals,

this has been modelled by administering different types of stressors repeatedly over a period of time, often for many weeks. Different chronic stress protocols have been used, and it is increasingly recognised that inter-individual differences exist between animals in terms of their vulnerability to chronic stress. This variability provides the possibility to elucidate the neurobiology of depression vulnerability and resilience. Importantly, the depressed-like FSL rat was found to be more sensitive than the FRL rat with regard to the anhedonia inducing effect of chronic mild stress (Pucilowski et al. 1993). However, a more detailed knowledge of the specific behavioural traits and associated neurobiological systems that mediate this increased sensitivity to stress is desirable.

Regarding the neurochemistry of depression vulnerability, Curzon (1988) proposed that 5-HT abnormalities in depression vary between subgroups, and can be either state or trait dependent, and that disturbances in 5-HT function underlie the vulnerability to depression. However, we do not know the precise molecular mechanisms by which the 5-HT deficits emerge. Given the capacity of pre- and postsynaptic mechanisms to compensate for changes by means of shifts in 5-HT availability and signal transduction, it appears unlikely that there is a single mechanism responsible for the deficiency in 5-HT function. A number of studies have examined the effect of chronic variable stress after lesioning of the 5-HT system. Two main approaches have been made to produce a lesion of the 5-HT system as the vulnerability model, one based on 3,4-methylenedioxymethamphetamine (MDMA) and another using para-chloroamphetamine (PCA).

MDMA is a phenylethylamine derivative that elicits the release of monoamines, particularly 5-HT, and inhibits monoamine reuptake and monoamine oxidase (Green et al. 2003). Repeated administration of MDMA induces partial degeneration of 5-HT neurons, but without major behavioural changes that might be expected if the 5-HT system were severely dysfunctional. It has, therefore, been considered that MDMA treatment leads to a possible subclinical state that could correspond to a depression vulnerability model (Cunningham et al. 2009; van Donkelaar et al. 2010). When MDMA was administered four times at 2 h intervals in the dose of 7.5 mg/kg to Sprague–Dawley rats, 5-HT transporter immunoreactivity was reduced to about 30 % of control (Cunningham et al. 2009). In these animals anxiety-like behaviour in the elevated plus-maze test was immediately increased, but had returned to control levels after 10 days of chronic mild stress. While this finding may be difficult to interpret as a stress diathesis effect, chronic mild stress also led to a learning impairment in the Morris water maze in the MDMA-pretreated rats. In another study, administration of 20 mg/kg of MDMA twice daily for 4 days to Wistar rats significantly reduced paroxetine binding to 5-HT transporters, indicative of partial loss of 5-HT terminals (van Donkelaar et al. 2010). This treatment produced a decrease in blood flow relative to cerebral metabolism as measured by deoxyglucose uptake. In comparison, acute tryptophan depletion, a technique that also reduces 5-HT availability in the brain and may predict vulnerability to depression in humans (Ruhe et al., 2007), increased blood flow relative to cerebral metabolism in MDMA-pretreated rats. These findings suggest that the 5-HT regulation of cerebrovascular tone may be altered after such

a partial lesion. It remains to be established whether this measure can be used in modelling depression vulnerability. However, information obtained from the model may be applicable to primates as MDMA exposure also alters behavioural and electrophysiological response to acute tryptophan depletion in rhesus monkeys (Taffe et al. 2003). Furthermore, a small study has suggested that former recreational MDMA users may indeed experience a higher level of depressive symptoms (MacInnes et al. 2001).

With the rationale that 5-HT deficits play a pivotal role at least in a subset of depressive syndromes (van Praag 2001), and that biological predispositions are likely to be complex and of quantitative rather than qualitative nature, a diathesis–stress model of applying chronic variable stress after administration of a low dose of PCA was introduced (Harro et al. 2001). PCA elicits a large release of 5-HT and temporary 5-HT depletion, followed by partial degeneration of 5-HT terminals and axons (Sanders-Bush et al. 1975). At variance with MDMA, a single dose of PCA is sufficient to elicit long lasting deficits in 5-HT. Our experience with monoamine neurotoxins is that large lesions are accompanied by compensatory changes that under stress lead to unexpected behavioural responses in conventional tests, and may thus reflect very different neurochemical balances which are hard to interpret in depression modelling (Kask et al. 1997; Harro et al., 1999). The size of lesion of the different neurotoxins depends on a number of factors including animal strain and housing conditions.

In our hands, PCA in a dose of 2 mg/kg consistently elicited a 20–30 % depletion of 5-HT (Häidkind et al. 2004). These PCA-induced partial 5-HT lesions, similar to chronic variable stress, increased anxiety in the social interaction test and reduced immobility at the first but not second session of forced swimming; the effect of combined PCA treatment and chronic variable stress was similar (Harro et al. 2001). Interestingly, sucrose intake in free-fed animals increased in the PCA-pretreated animals during chronic variable stress. This result is reminiscent of Wurtman's suggestion that "atypical" depression, that includes increased craving for carbohydrates, is specifically caused by a deficit of 5-HT in stressful conditions (Wurtman and Wurtman 1996). Both increased sucrose intake and increased struggling during swimming observed in animals treated with PCA plus stress were prevented by administration of citalopram (Tõnissaar et al. 2008). This suggests that the behavioural vulnerability was associated with a 5-HT deficiency.

9 Personality as a Vulnerability Factor

Of the four major risk factors of depression identified by epidemiological studies (Fava and Kendler 2000), temperament or personality represents the vulnerability side in the diathesis–stress approach. Personality traits, especially neuroticism, are related to affective disorders (e.g., Lesch 2007), and longitudinal twin studies suggest that neuroticism is strongly associated with a genetic risk of major depression (Kendler et al. 2006). Personality traits are defined as enduring patterns

of perceiving, relating to, and thinking about the environment, and hence, as predispositions to react to it. What has been established on the structure of personality suggests that similar constructs can be applied across mammalian species (Davis and Panksepp 2011). Some of the animal models of depression vulnerability may, therefore, already implicitly incorporate the factor of neuroticism, or synonymously, low emotional stability. Unfortunately, most of the established vulnerability models have used other selection principles, and therefore reflect rather a constellation of traits. Nevertheless, the data available suggest that new vistas may be opened through research on temperamental differences in animal models.

One of the most extensively exploited models of inter-individual differences is the high responder/low responder (HR/LR) to novelty approach. HR/LR rats are classified on the basis of the level of spontaneous locomotor activity in a novel environment, and in its original formulation the model was proposed as a measure of vulnerability to drug abuse (Piazza et al. 1989). A variety of selection principles have been reported, and HR/LR rats have been recently selectively bred (Stead et al. 2006). Given that psychomotor retardation is an important symptom of depression, the LR rats possess some face validity as a depression vulnerability model; furthermore, the bred LR rats were found to be more anxious. Bred LR rats developed a reduction in sucrose preference by the second week of stress exposure, and a further dramatic decline by the third week (Stedenfeld et al. 2011), suggesting that the LR animals are indeed more predisposed to react to chronic stress. However, another study has reported opposite findings in a social defeat paradigm: 2 weeks after four daily consecutive social defeat exposures, HR rats exhibited not only higher anxiety levels, but also reduced body weight gain and sucrose preference, and marked social avoidance (Duclot et al. 2011). In a somewhat different investigation, chronic variable stress during adolescence elicited antidepressant-like effects (reduced immobility in the forced swimming test) in the HR rats, this being accompanied by epigenetic activation of the hippocampal BDNF (Oztan et al. 2011).

Since neuroticism is often expressed as heightened anxiety response, measurement of anxiety may offer a means to create a depression vulnerability model based around this trait construct. Inter-individual differences in anxiety-related activity as measured in elevated plus maze, open field or social interaction test have been established, and several interesting neurobiological leads for modelling depression vulnerability have been derived from these studies (see Harro 2010 for a review). Nevertheless, testing of an explicit diathesis–stress model remains rare as yet.

With the aim of clustering two landmark symptoms of depression, negative emotion and low motivation, we created the exploration box test that separates rats bimodally into high anxiety/low exploratory drive and low anxiety/high exploratory drive groups (Mällo et al. 2007a). These phenotypes are persistent, and the low exploring (LE) rats appear to be more responsive to acute stress as compared to the high exploring (HE) rats in a number of tests. When LE and HE rats were submitted to chronic variable stress, this did not alter the defining phenotype and led to largely similar effects in both groups (Matrov et al. 2011). In fact, in a number of studies comparing stress effects on animals with different expression of

a trait, the defining phenotype survives chronic stress but other behavioural and neurochemical differences do not (see Harro 2010 for review).

Interestingly, there were many differences between the LE and HE rats in terms of gene expression patterns as measured on the Illumina microarray platform in cortex, hippocampus and raphe (Alttoa et al. 2010), with all of these differences linked with anxiety or depression in the expected direction. Notwithstanding this, LE and HE rats behaved similarly in a number of tasks, suggesting that higher expression of a significant number of "anxiety or depression genes" does not cumulatively produce general dysfunction. Furthermore, both LE and HE rats were able to adapt to 3 weeks of chronic mild stress, in terms of recovery of reduced sucrose intake (Matrov et al. 2011).

While cross-species affective neuroscience has recently cast doubt on the grouping together of several basic emotions under one umbrella measured as neuroticism, high negative emotionality or low emotional stability (Davis and Panksepp 2011), neuroticism has at least featured rather consistently in personality studies, and reliable scales are broadly used. Much less is known on the possible role of low positive emotionality, even though positive affect is not simply the other pole of negative affect but rather orthogonal to it, and diminished positive affect is a central feature to depression (Clark and Watson 1991; Forbes and Dahl 2005). Response to antidepressant treatment was found to be predicted better by an increase in experiencing positive emotions than a decrease in negative emotionality (Geschwind et al. 2011).

A positive affective state can be measured in rats by recording 50 kHz ultrasonic vocalisations in response to tickling-like manual stimulation (Burgdorf and Panksepp 2001). There is a large inter-individual difference in responsivity, and these differences are persistent (Mällo et al. 2007b). When male rats with higher and lower levels of 50 kHz chirping (HC and LC, respectively) were submitted to chronic variable stress in adulthood, it was found that compared to HC rats, the stressed LC rats exhibited increased levels of 22 kHz vocalisations (indicative of negative emotionality), an earlier and more stable reduction of weight gain, reduced sucrose intake and increased immobility in the forced swimming test (Mällo et al. 2009). This vulnerability to chronic stress in the LC rats was also reflected in changes in cerebral oxidative metabolism. Also, after chronic variable stress LC rats had a more reactive HPA response to stress, and altered regulation of extracellular levels of 5-HT (Raudkivi et al. 2012). This animal model, thus, supports the notion that low inherent positive affectivity can serve as a diathesis for affect-related disorders.

10 Vulnerability Based on Post hoc Assessment

The salience of understanding the neurobiology of inter-individual differences for biological psychiatry and psychopharmacology is increasingly recognised (Harro 2010). A major impact relevant to depression studies has been influential report of

Berton and colleagues (Berton et al. 2006) on the role of brain-derived neurotrophic factor (BDNF) in the mesolimbic dopamine pathway in response to social defeat stress. This study turned the fact that not all animals react equally to stressful stimuli into an advantage. A comparison of mice with reduced social engagement after repeated defeat with their resilient counterparts revealed a number of alterations associated with defeated behaviour, including reduced sucrose intake. Since then many studies have identified mice and rats as social stress sensitive or -resilient, using quite a variety of methods of stress induction combined with criteria for defining the vulnerability (e.g., Schmidt et al. 2010; Kanarik et al. 2011). Other researchers have classified rats into vulnerable and resilient groups based on sucrose intake in the chronic mild stress paradigm (Bergström et al. 2008). These studies have identified a number of neurobiological differences between stress sensitive and -resilient animals. In a full diathesis–stress model, Strekalova et al. (2004) examined C57BL/6 mice in a resident-intruder paradigm, and submitted both the submissive and non-submissive animals to a variant of chronic variable stress for 4 weeks. They found that only submissive mice developed anhedonia, increased immobility in the forced swimming test and reduced exploratory behaviour.

11 The Sex/Gender Factor

It is well-known that prevalence of depression is higher in females than males, and sex/gender has been specified as a major risk factor of depression in epidemiological studies (Fava and Kendler 2000). At the first glance it would appear less important for animal model development because the causal link is hard to delineate, and some of the variance in prevalence may be socially constructed (i.e. rather the gender than sex issue). Also, depression quite frequently occurs in males. Nevertheless, the sex/gender factor would become extremely important for model building if the neurobiological basis of depression in males and females were different. Evidence is accumulating that this may be the case (Shaffery et al. 2003), and therefore comparison of stress effects in vulnerable male and female animals appears an important avenue. Some studies that have compared effects of prenatal or chronic variable stress in males and females have rather unexpectedly found that routine behavioural tests indicate higher vulnerability in males (Goel and Bale 2009; Mällo et al. 2009; Sun and Alkon 2006). Considering that most of the studies on modelling depression have been carried out on male animals, there is a possibility that behavioural readouts that are especially sensitive to negative affect and anhedonia in males have become preferred by researchers.

One type of life event unique to females can lead to vulnerability to depression; the post-partum period is the time of greatest risk for women to develop major depression (Goodman 2007). Animal models of post-partum depression make use of knowledge on hormonal changes around delivery, or apply chronic stress during pregnancy to elicit behavioural or neurobiological changes observed in other

models of depression (Brummelte and Galea 2010). However, in this respect it appears that the diathesis–stress concept has not been tested as yet.

12 Limitations and Caveats

Coming closer to the pathogenetic principles, diathesis–stress models should offer advantages in the discovery of depression endophenotypes, and also for drug discovery if they prove to be robust predictors of clinical efficacy. However, diathesis–stress models require an increased number of experimental groups and animals, and thus recruitment of additional resources. Furthermore in a true vulnerability model, at the statistical level interaction effects are expected and this requires greater statistical power to achieve significance.

Naturally, as with any animal model of human psychopathology, painstaking work is required to validate the diathesis–stress-based models. As noted above, stressful life events are likely to 'immunize' the organism towards further impacts. Recently, a series of experiments combining prenatal stress with chronic mild stress in adulthood revealed a number of changes in behaviour, as well as cortical structure, that were suggestive of protective adaptations on prenatally stressed rats (Michelsen et al. 2007; van den Hove 2006). Another factor to be considered in diathesis–stress research is familial aggregation, that genetic predisposition which can be moderated by environmental conditions in relation to the genetic similarity of parents and offspring. For instance, two inbred mouse strains, BALB/c and C57BL/6, have often been compared as genetically different strains with more versus less anxiety behaviour and stress sensitivity. In recent research, BALB/c mice have also been described as poor mothers with inferior nest building, less time spent on the nest and longer pup retrieval latencies in experiments. Moreover, this mothering behaviour has been suggested to affect gene methylation patterns (Anisman et al. 2008; Tarantino et al. 2011). Similarly, the FSL rats have been reported to exhibit relatively poor mothering style (Lavi-Avnon et al. 2005). Cross-fostering experiments have shed some light on the relative contribution of genotype and mothering style (Anisman et al. 2008), but this research area is still in its early stage.

A further issue in model development is the decision regarding which readouts to use. Until recently, it prevailed that a model of depression is appropriate if it has behavioural similarity with the human clinically diagnosable condition. This is now being challenged by the idea that rather than trying to recreate or mimic the complete spectrum of symptoms comprising the syndrome of depression, animal models should focus on major constructs such as negative affect, positive affect or physiological hyper arousal (Frazer and Morilak 2005). Another view is that major well-understood symptoms or symptom clusters can be targeted (Fernando and Robbins 2011). As a further refinement of symptom or symptom cluster-based models, endophenotype-specific models have been advocated (Cryan and Slattery

2007). This approach requires identification of biomarkers that relate to the etiopathogenetic process of depression development.

While the history of biological psychiatry has seen an abundance of putative biomarkers for depression come and go, the advance of in vivo neuroimaging methods and refinement of selection of subjects and experimental tasks, should increase the probability of discovery of more reliable indicators. For example using functional magnetic resonance imaging (fMRI) and reward processing tasks, it was found that childhood adversity with increased symptoms of anhedonia and depression is associated with blunted subjective responses to reward-predicting cues as well as a weaker response in the left globus pallidus (Dillon et al. 2009). Of course, the question remains whether it is any longer depression that is being modelled, if the focus shifts to symptoms. We should probably return in future to attempts to model the whole syndrome, but this requires better understanding of the human pathology. If the underlying molecular mechanisms are well known, it will be more feasible to consider animal models of the entire clinical disorder (Fernando and Robbins 2011).

In conclusion, the etiopathogenetic diathesis–stress approach to developing animal models of depression vulnerability appears promising and has yielded a deeper understanding of neurobiology of depression as a subject to inter-individual differences. Furthermore, systematic studies should clarify whether or not this approach can improve antidepressant drug screening, detect compounds with novel mechanisms of action with low false positive rate and advance more personalised medicine.

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