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Genetic Mouse Models of Depression

Christopher Barkus

Abstract This chapter focuses on the use of genetically modified mice in investigating the neurobiology of depressive behaviour. First, the behavioural tests commonly used as a model of depressive-like behaviour in rodents are described. These tests include those sensitive to antidepressant treatment such as the forced swim test and the tail suspension test, as well as other tests that encompass the wider symptomatology of a depressive episode. A selection of example mutant mouse lines is then presented to illustrate the use of these tests. As our understanding of depression increases, an expanding list of candidate genes is being investigated using mutant mice. Here, mice relevant to the monoamine and corticotrophin-releasing factor hypotheses of depression are covered as well as those relating to the more recent candidate, brain-derived neurotrophic factor. This selection provides interesting examples of the use of complimentary lines, such as those that have genetic removal or overexpression, and also opposing behavioural changes seen following manipulation of closely related genes. Finally, factors such as the issue of background strain and influence of environmental factors are reflected upon, before considering what can realistically be expected of a mouse model of this complex psychiatric disorder.

Keywords Knockout mice · Forced swim test · Serotonin transporter · Noradrenaline transporter · CRF · BDNF

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Contents

1 Introduction

Experimental animal models allow for methods of study into disease and treatment that would be unethical, impractical or otherwise impossible in humans. By using experimental animals, the molecular underpinnings of disorders and their treatment can be investigated, but modelling complex psychiatric diseases in rodents is problematic.

While there are other ways to model depressive-like phenotypes in rodents, such as olfactory bulbectomy (Song and Leonard 2005) and chronic stress paradigms (Willner 2005, but see also Forbes et al. 1996), this chapter will focus on the use of mutant genetic mouse lines in investigations of emotional behaviour as well as what constitutes a behavioural model of depression in rodents.

2 Depressed Mice?

A major depressive episode in humans comprises a number of different core symptoms and biological changes, but it is invariably a multifaceted event. Of the many symptoms that can comprise a depressive episode, some are simply impossible to model in rodents. These include the subjective feelings of fatigue and guilt, as well as suicidal ideation. However, for many core symptoms there are analogous models, which are reviewed in detail elsewhere (e.g., Crawley 2000). Here, some of these models will be noted in brief to contextualise a subsequent more detailed discussion of the work done using putative mutant mouse models of depression.

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A good rodent model of depression would feature many of the depressive-like behaviours detailed below, as well as possibly some of the associated physiological changes commonly seen in depressed individuals, such as altered EEG sleep architecture. When the depressive-like phenotype detected in a mutant mouse model can also be reversed by clinically effective antidepressants, this adds to the validity of the model.

2.1 Depressed Mood

To avoid suggesting we can measure mood *per se* in rodents, the term "behavioural despair" is often applied to tests sensitive to antidepressant treatment. The two most commonly used tests for behavioural despair in mice are the forced swim test and the tail suspension test.

2.1.1 The Forced Swim Test

The forced swim test was first developed in the late 1970s as a test sensitive to antidepressant activity in both rats and mice (Porsolt et al. 1977a, b, 1978a, b). At its simplest, this test involves placing the rodent in a non-escapable cylinder of water and monitoring the resultant behaviour. Measurement of the time spent actively moving in an attempt to escape as well as the time spent passively immobile, are thought to provide a way of quantifying the rodent's propensity toward helplessness (summarised in Cryan et al. 2005b). An important indicator of the validity of the test is that the time spent immobile is typically decreased by clinically effective antidepressant drugs.

Activity during non-immobile phases is thought by some to have separate underlying neurobiological mechanisms. In particular, Denke and colleagues have proposed that noradrenergic mechanisms mediate increased climbing, whereas serotonergic mechanisms mediate increased swimming (Detke et al. 1997, 1995; Detke and Lucki 1996).

The specifics of how this test is carried out vary somewhat between studies and labs, but the typical duration of the forced swim test is 5–6 min. A day or so prior to the test, there may also be a pre-exposure to the non-escapable cylinder of water, which acts as a stressor and may improve the sensitivity of the test both to pharmacological and genetic manipulations. Importantly, the test ought to be paired with an assessment of general locomotor activity to exclude the potential confounding effect of hyperactivity induced by the genetic manipulation or pharmacological agent.

2.1.2 The Tail Suspension Test

Similar to the forced swim test, the tail suspension test involves recording immobility of mice exposed to an inescapable stressful situation, in this case

suspension by the tail from a fixed structure, usually for 6 min (Steru et al. 1985). This test has been extensively validated pharmacologically (see Cryan et al. 2005a for review) and can be used alongside, or as an alternative to, the forced swim test.

As with the forced swim test, independent assessments of locomotor activity should be made to ensure the selectivity of any changes in immobility. A further issue with this test is the curious ability of mice on the C57Bl/6 background to climb up their own tails, therefore confounding assessment of the time spent immobile (Mayorga and Lucki 2001). Those mice that excessively display this acrobatic attempt to escape usually are excluded from further analysis, which can lead to sampling bias.

2.2 Anhedonia

Anhedonia is also a core symptom of depression that can be measured in rodents, and is sometimes overlooked in work with mutant mouse lines. Anhedonia is typically assessed in rodents by measuring preference for sucrose or saccharine over water (Papp et al. 1991). Reduced sucrose/saccharine preference is a typical characteristic of rodents exposed to chronic stress paradigms, and has also observed in genetic mouse models (El Yacoubi et al. 2003).

Decreased social interaction is often associated with anhedonia, as a reduction in socialising is specifically mentioned in the DSM criteria under anhedonia (DSM IV-TR 2000). In rodents, social behaviour can be quantified in a number of ways, the simplest being to place two unfamiliar mice in an open arena for a fixed period and measure the time spent engaged in active social interaction. However, the level of sociability of mice in such a paradigm is affected by other behavioural drives such as exploration of the environment or a reluctance to explore due to high anxiety. Social interaction may therefore not offer an absolute measure of anhedonia, but is, nonetheless, interesting as a naturalistic behaviour that encompasses certain behaviours relevant to depression.

2.3 Anxiety

Although anxiety disorders form a class of psychiatric illness in their own right, anxiety is also highly co-morbid with clinical depression (DSM IV-TR 2000; Zimmerman et al. 2000). Many tests of anxiety exist in rodents that have been developed and validated using clinically effective anxiolytic drugs such as benzodiazepines. These tests include the elevated plus maze (Handley and Mithani 1984; Lister 1987; Pellow et al. 1985), open field (Hall 1936; Treit and Fundytus 1988) and light/dark box (Blumstein and Crawley 1983; Crawley and Goodwin 1980; Crawley 1981). These tests typically rely on measurement of a conflict between competing behaviours in rodents; for example, on one hand to explore novel environments and on the other to avoid possibly threatening situations such as open, brightly lit areas which trigger an innate fear of predators.

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3 Genetic Mouse Models of D

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Assessments of locomotor activity during these tests can provide a useful control to ensure that apparently altered levels of anxiety are not secondary to changes in general activity. Such assessments include distance moved across the arena, closed arm entries (elevated plus maze) or light/dark transitions. These assessments are best paired with an independent measurement of locomotor activity, to ascertain if changes in movement are a likely product of being placed in an anxious situation; a mouse may move less because it is anxious and thus make fewer transitions, for example.

2.4 Other Symptoms

In addition to the measures of depressive-like symptoms mentioned above, many other symptoms characteristic of a depressive episode can be modelled in rodents. For example, alterations in weight and feeding behaviour can easily be assessed, as can disrupted activity over the diurnal cycle. Further to this, sleep architecture, which is often disturbed in depressed patients (Steiger and Kimura 2010), can be assessed in rodents using implanted EEG electrodes.

There are many cognitive parameters that may be disrupted by a depressive episode, including decisiveness and concentration/attention. One task that is thought to give a measure of attention in rodents is the serial reaction time task (Robbins 2002), although this task is more commonly used in rats than mice. Tests of spatial memory are often substituted for measures of attention, although this seems to conflate quite different cognitive processes.

Further tests may also be helpful to probe specific questions about the nature of depressive-like state. For example, fear conditioning can be used as a model of aversive learning which may be relevant to the underpinnings of depression. There are also physiological disturbances often associated with depression in humans that can be easily measured in rodents such as hypothalamic-pituitary adrenal (HPA) axis functionality.

The remainder of this chapter will illustrate how the behavioural tasks detailed above can provide phenotypic measures of depressive-like behaviour in genetic mouse models.

3 Genetic Mouse Models of Depression

Many mutant mouse lines have been created on the basis of the growing knowledge of genes implicated in the pathogenesis of depression and its treatment. The majority of these lines involve the inactivation of a candidate gene for depression, resulting in an antidepressive-like phenotype. Examples of such models include 5-HT_{1A} receptor knockout mice (Heisler et al. 1998; Parks et al. 1998; Ramboz et al. 1998) and noradrenaline transporter knockout mice (Xu et al. 2000). The number of genetic models that result in depressive behaviours is much fewer, although there are still examples across several neurobiological systems.

A selection of these are discussed below along with some mutant mice that display antidepressive-like behaviour that provide interesting counterpoints to mice with a depressive-like phenotype.

New mutant mouse models and gene targets of interest are constantly being developed and investigated. The focus here will be on models relating to the established monoamine hypothesis of depression and also the stress hypothesis centred on corticotrophin-releasing factor (CRF). Also discussed is another hypothesis of depression set around brain-derived neurotrophic factor (BDNF), a more recent and contentious player in mood disorders. Each of these areas provides examples which illustrate the usefulness of the behavioural tests noted in determining the extent of the depressive phenotype of the model. Other reviews and perspectives of this field can also be found in the literature (e.g. Cryan and Mombereau 2004; Gardier et al. 2009).

3.1 5-HT Transporter

The serotonin (5-hydroxytryptamine or 5-HT) system has long been implicated in the pathogenesis of depression (Schildkraut 1965) as well as its treatment as exemplified by the current front-line antidepressant drugs being selective serotonin reuptake inhibitors (SSRIs). Since these agents, like many other antidepressant drugs, act by blocking the 5-HT transporter (Owens et al. 1997; Owens and Nemeroff 1994), it places the latter as an important candidate gene for depression. A further reason to study the 5-HT transporter gene is that there is a large, naturally occurring variation in expression levels of this gene in the human population. One driver of this variation is thought to be a common insertion/deletion polymorphism in the promoter region of the gene (5-HTTLPR polymorphism) that generates short (s) and long (l) alleles which are either low (s/s) or high (l/l) expressing, at least in cell-based models (Heils et al. 1996; Lesch et al. 1996). It is thought that individuals with the low expressing variant of the 5-HT transporter gene are predisposed to mood and anxiety disorders (Furlong et al. 1998; Lasky-Su et al. 2005; Lotrich and Pollock 2004), although this remains contentious (e.g. Anguelova et al. 2003).

There is some disagreement regarding the impact of the genetic polymorphisms and actual levels of functional 5-HT transporter protein in vivo (Mann et al. 2000; Naylor et al. 1998; Rhodes et al. 2007; Shioe et al. 2003), which complicates interpretation of the reported 5-HT transporter genotype–phenotype associations. However, a reliable alteration in 5-HT transporter levels between individuals is something that can be generated genetically in mice. Moreover, the high degree of genetic homogeneity, within an experimental cohort of transgenic mice, is a major help in reducing the confounds of a high level of genetic heterogeneity in a human population, in addition to variation in the gene of interest. Furthermore, gene x environment interactions can also be better controlled with experimental animals than with human participants.

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For investigations of the role of variation in the 5-HT transporter on behaviour in mice both knockout and overexpressor lines exist, thereby enabling the study of a range of expression levels in an otherwise well-controlled genetic system. Genetic knockout of the 5-HT transporter might be predicted to have the same effect as pharmacological blockade of the 5-HT transporter; that is, 5-HT transporter knockout mice would be expected to behave similar to wild-type mice treated with an SSRI. However, if we consider the findings from human gene association studies that individuals with the low expressing variant of the 5-HT transporter gene are predisposed to mood and anxiety disorders, then we might expect 5-HT transporter knockout mice to show an anxious, depressive-like phenotype.

Several laboratories developed 5-HT transporter knockout mice (first produced by Bengel and colleagues 1998) but conflicting results were found in the early studies. When bred onto a 129S6/SvEv line 5-HT transporter knockout mice were found to have increased immobility during single exposure to the forced swim test (Lira et al. 2003) but, conversely, decreased immobility in the tail suspension test (Holmes et al. 2002; Lira et al. 2003). Additionally, these mice appeared more anxious in a novelty-suppressed feeding paradigm but did not show robust differences from wild-type mice on the elevated plus maze (Holmes et al. 2003b; Lira et al. 2003).

In comparison, 5-HT transporter knockout mice generated from mice on a C57Bl/6 J-129 Sv mixed background, showed a decrease in immobility in the tail suspension test but no change in a two exposure form of the forced swim test (Perona et al. 2008). The latter mice showed no change in sucrose preference. However, on a pure C57Bl/6 background, 5-HT transporter knockout mice showed a robust increase in anxiety across a number of tests (Holmes et al. 2003a, b; Kalueff et al. 2007; Zhao et al. 2006; Line et al. 2011; but see also Adamec et al. 2006). These mice also showed an increase in immobility in both the tail suspension test (Zhao et al. 2006; but see also Holmes et al. 2002) and forced swim test (Wellman et al. 2007), although the latter depressive-like phenotype required multiple exposures to the test. These mice did not demonstrate altered sucrose preference (Kalueff et al. 2006).

Whilst the contrasting effect of 5-HT transporter knockout in tests of behavioural despair seem confusing, a robust pattern of increased anxiety can be seen across strains and tests. The results from the forced swim test across all strains suggest a depressive-like phenotype, albeit a subtle one that is only detectable following repeated swim stress exposure. The findings from the tail suspension test, however, are less easy to explain with antidepressant effects being detected in mice on either a 129 or mixed.

5-HT transporter overexpressor mice have also been developed and characterised, and the phenotype of these mice add much strength to the outcome of the knockout studies, at least in terms of the anxiety data. Thus, the 5-HT trausporter overexpressing mice were found to have reduced anxiety, the opposite of what is generally seen in the knockout lines (Jennings et al. 2006; Line et al. 2011). In studies of 5-HT transporter variation, these mice offer an interesting and valuable

contrast to the knockout mice and allow for a wide range of expression levels to be explored.

Overall, a likely important factor, in some of discrepant findings regarding the 5-HT transporter knockout mice, is the background strain of the mouse used to construct the knockout. Ironically, this indicates that the genetic heterogeneity that may account for conflicting results in human studies, also influence the outcome of the genetic mouse studies. Further discussion of the issue of background strain in mutant mice can be found later in this chapter.

3.2 Noradrenaline

Noradrenaline has also long been associated with depression. There is evidence for alterations of noradrenaline and its receptors in both depression pathophysiology and in response to antidepressant administration (e.g., Ordway et al. 2003; Deupree et al. 2007; see also chapter by Sharp in this volume). Perhaps the most compelling evidence for a role for noradrenaline in depression is that the noradrenaline transporter is a major target for tricyclic antidepressant drugs as well as recently developed selective noradrenaline reuptake inhibitors (SNRIs). Noradrenaline is also heavily involved in stress, which is a well-known risk factor for depression.

3.2.1 Adrenoceptors

Receptors for noradrenaline (adrenoceptors) are found throughout both the central and autonomic nervous systems. Indeed, many of the adrenoceptor mutant mice were initially constructed for investigations into the cardiovascular system. While the focus here is on behavioural changes in these mice that are relevant to modelling depression, changes in the periphery should not be forgotten as possible confounds or, indeed, have direct relevance to changes emotionality and stress levels.

Selective pharmacological tools for several subtypes of adrenoceptor are yet to be developed and so much of what is known about the actions of some of these receptors are derived from studies on adrenoceptor mutant mice. For example, drugs non-selective for the different types of α_2 adrenoceptor have been found to have wide-ranging effects that include altered sedation and cardiovascular changes, which have complicated interpretation of many behavioural measures. These effects are largely the result of the α_{2A} adrenoceptor as shown through use of α_{2A} knockout mice (Lakhlani et al. 1997).

In tests of depressive-like behaviour, α_{2A} adrenoceptor knockout mice displayed increased immobility in the forced swim test, mediated by decreased climbing and not changes in swimming (Schramm et al. 2001). Also these mice appeared more anxious in both the elevated plus maze (Lahdesmaki et al. 2002)

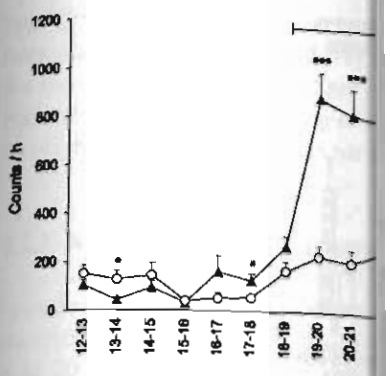

Fig. 1 The locomotor activity of wild t period following a 2 h habituation period. activity in response to the onset of the da adrenoceptor knockout mice. This may b during a depressive episode (from Lahde

and light/dark box, but the latter o 2001). The α_{2A} adrenoceptor knock activity across the diurnal cycle (s wake cycle, as seen in depression. activity may be due to the influence melatonin (Lahdesmaki et al. 2002)

The study by Schramm and co which an antidepressant drug effect when a two exposure form of the fo exposure (Schramm et al. 2001). Th minor changes to the forced swim t of the behavioural test.

In contrast to the α_{2A} adrenocept mice were found to display decr (Sallinen et al. 1999). Again, the s was dependent on pre-exposure to t the role of α_2 adrenoceptor subtype overexpressor mice were shown to test (ibid.).

Overall, these data strongly impli measure of depressive-like behavio appearing to be antidepressant and depressive. While further testing knockout and overexpressor lines of allow for in-depth exploration of th behaviour.

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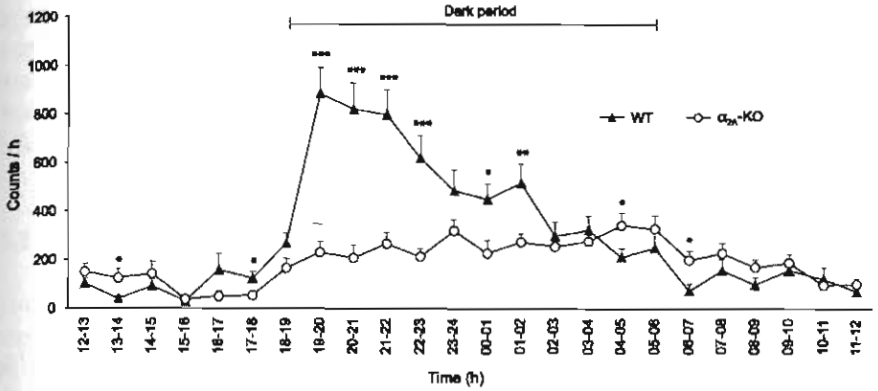

Fig. 1 The locomotor activity of wild type and α_{2A} adrenoceptor knoekout mice over a 24 h period following a 2 h habituation period. Wild-type mice show a dramatic increase in loeomotor activity in response to the onset of the dark period of the diurnal eyele but this is absent in α_{2A} adrenoceptor knockout mice. This may be relevant to the disruption of circadian rhythms seen during a depressive episode (from Lahdesmaki et al. 2002)

and light/dark box, but the latter only following injection stress (Schramm et al. 2001). The α_{2A} adrenoceptor knockout mice also displayed a flattened pattern of activity across the diurnal cycle (see Fig. 1), suggestive of disruptions to sleep/wake cycle, as seen in depression. It is suggested that altered diurnal pattern of activity may be due to the influence of the noradrenaline system on the synthesis of melatonin (Lahdesmaki et al. 2002).

The study by Schramm and colleagues provides an interesting example in which an antidepressant drug effect (imipramine) was seen in wild-type mice only when a two exposure form of the forced swim test was used and not after a single exposure (Schramm et al. 2001). This highlights the importance of how seemingly minor changes to the forced swim test protocol can markedly alter the sensitivity of the behavioural test.

In contrast to the α_{2A} adrenoceptor knockout mice, α_{2C} adrenoceptor knockout mice were found to display decreased immobility in the forced swim test (Sallinen et al. 1999). Again, the sensitivity of this test to detect this difference was dependent on pre-exposure to the swim test (see Fig. 2). To further validate the role of α_2 adrenoceptor subtypes in the forced swim test, α_{2C} adrenoceptor overexpressor mice were shown to have increased levels of immobility in this test (ibid.).

Overall, these data strongly implicate α_2 adrenoceptors in the forced swim test measure of depressive-like behaviour, with α_{2A} adrenoceptor-mediated activity appearing to be antidepressant and α_{2C} adrenoceptor-mediated activity being pro-depressive. While further testing needs to be done, the availability of both knockout and overexpressor lines of these adrenoceptor-specific mutant mice will allow for in-depth exploration of the role that these receptors play in emotional behaviour.

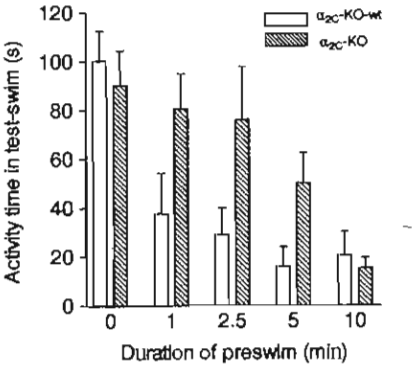

Fig. 2 The time spent active during a 5 min forced swim test following various lengths of prior exposure 24 h previously in wild type and α_{2C} adrenoceptor knockout mice. Prior exposure to forced swimming reduces activity in mice. In the case of this study, this effect was more dramatic in wild-type mice and so revealed an anti-depressive-like phenotype in α_{2C} adrenoceptor knockout mice. This suggests the use of a pre-swim session may be important in determining the sensitivity of the forced swim test. Taken from Sallinen et al. (1999)

It is worth noting, however, that other non-mood-related alterations in behaviour have been noted in some of these mouse lines including altered pre-pulse inhibition performance in both the α_{2C} adrenoceptor knockout and overexpressor mice (Sallinen et al. 1998). Nonetheless, these results have led to the α_{2C} adrenoceptor being proposed as a possible target for future therapeutic drugs that would lack the sedative effects of drugs that target α_{2A} adrenoceptors (Sallinen et al. 1999). Whether such agents would be sufficiently specific for the treatment of depression without having more wide-ranging effects remains to be seen.

The role of α_1 adrenoceptors in depressive behaviours has also been explored using mutant mice. In this case, instead of the receptor being knocked out, mice expressing a constitutively active form of the receptor have been developed. Such mutants have been constructed for both α_{1A} (Rorabaugh et al. 2005) and α_{1B} (Zuscik et al. 2000) adrenoceptors. The use of these mice has revealed complimentary alterations in behaviour. Thus, mice with constitutively active α_{1A} adrenoceptors having decreased immobility in both the forced swim test (Doze et al. 2009) and tail suspension test (Doze et al. 2009, 2011), whereas mice with constitutively active α_{1B} receptors showed increased immobility in these tests (Doze et al. 2009). The increased immobility in these tests of the latter mice contrasted with their general hyperactivity in an open field (with α_{1A} adrenoceptor constitutively active mutant mice having levels of locomotion similar to their wildtype controls). The anxiety profile of the α_{1A} adrenoceptor mutants, however, is unclear (Doze et al. 2009, 2011), the α_{1B} adrenoceptor mutant line do not appear to have altered levels of anxiety (Doze et al. 2009).

This work using sub-type specific manipulations of adrenoceptors reveals complex, opposing actions of these receptors in affective behaviour. The possibility of selectively targeting specific adrenoceptor populations using pharmacological agents is something yet to be taken advantage of in treatment of depression owing to the lack of

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3.2.2 Noradrenaline Transporter

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3.3 CRF-Related Models

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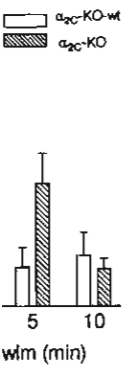

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appropriate drugs. While some current antidepressants act to block the reuptake of noradrenaline, and so affect activity at all adrenoceptors, targeting specific subtypes of the receptors for noradrenaline may produce more effective future therapeutics. This research provides an interesting example of how work with genetically altered mice has highlighted possible targets for future antidepressant drug development.

3.2.2 Noradrenaline Transporter

Noradrenaline transporter knockout mice display an antidepressant phenotype in both the forced swim test (Perona et al. 2008; Xu et al. 2000) and tail suspension test (Perona et al. 2008). This is, in spite of, also being found to be hypoactive (Perona et al. 2008; Xu et al. 2000). However, no alteration was seen to their sucrose preference at a range of sucrose concentrations (Perona et al. 2008). While the generally antidepressant-like phenotype is in line with the effects of tricyclic antidepressants and SNRIs that block the noradrenaline transporter, the data are in contrast to the findings from 5-HT transporter knockout mice which do not have an antidepressant phenotype (see above).

This difference between these noradrenaline and 5-HT transporter knockout lines is a curious one. The behavioural phenotype of the 5-HT transporter knockout mice, which is, in simple terms, the opposite to that seen following acute SSRI treatment, is often explained by a developmental origin of the phenotype, citing the role 5-HT has during development (Gingrich et al. 2003).

To examine the influence of the 5-HT and noradrenaline transporters in brain development, SSRIs and SNRIs have been administered to mice shortly after birth. Early SSRI treatment produced persistent behavioural changes including increased anxiety in adulthood (Ansorge et al. 2004, 2008). SNRI treatment, however, did not result in the same life-long changes (Ansorge et al. 2008). This finding may account for the contrasting phenotypes in the 5-HT transporter and noradrenaline transporter knockout mice; early 5-HT transporter blockade leads to (over-)compensatory changes that result in permanently altered emotionality, whereas early noradrenaline transporter blockade does not. This might help to explain why life-long 5-HT transporter blockade (5-HT transporter knockout) has the opposite effect to what would be expected from SSRI treatment, whereas life-long noradrenaline transporter blockade (noradrenaline transporter knockout) has effects similar to SNRI treatment.

The phenotypes of the transporter mutant mice illustrate the often complex relationship between pharmacological and genetic interventions, and also emphasises the importance of developmental effects of gene knockout on adult emotional behaviour.

3.3 CRF-Related Models

The role of corticotrophin-releasing factor (CRF) is traditionally seen as being imbedded in the hypothalamic-pituitary adrenal (HPA) axis, in that this neuropeptide is released from the hypothalamus to stimulate release of adrenocorticotrophic

hormone (ACTH) from the pituitary that subsequently leads to the release of corticosteroid "stress hormones" from the adrenal glands. This process may in itself be important in depression, but receptors for CRF are expressed throughout the brain, not just in the hypothalamus. Therefore, extra-hypothalamic actions of CRF may also be important in the pathophysiology of depression.

CRF acting at CRF_1 receptors in limbic brain areas, such as the cerebral cortex, hippocampus and amygdala, is thought to lead to many of the behaviours associated with anxiety and depression (Holsboer 2000). This signal is modulated by a second class of CRF receptors, CRF_2 receptors, which bind CRF-like proteins known as urocortins. Thus far, three urocortins have been characterised; urocortin1 (Donaldson et al. 1996; Vaughan et al. 1995), urocortin2 (Reyes et al. 2001) and urocortin3 (Lewis et al. 2001). These peptides are expressed throughout the CNS in overlapping but unique patterns. Generally, activity at CRF_2 receptors is thought to dampen the effects of CRF_1 receptor activity and so is broadly anti-depressive and anxiolytic. Further modulation of this system is achieved by the CRF binding protein which sequesters all CRF-like proteins and prevents them binding to the receptors.

Mutant mouse lines with greatly increased CRF activity have been found to exhibit a Cushing's-like cluster of symptoms. For example, CRF overexpressor mice were found to have increased anxiety (Heinrichs et al. 1997; van Gaalen et al. 2002), but also thin skin, alopecia and altered fat and muscle deposition (Stenzel-Poore et al. 1992). Despite these many changes, CRF overexpressor mice provide an example of a mouse line that has been tested on some important but often ignored components of depressive-like behaviour. For instance, CRF mice have been shown to have a deficit in the serial reaction time task, a highly involved cognitive task that may be more relevant to the deficits seen in depression than assessments of, for example, spatial memory (van Gaalen et al. 2003).

CRF knockout when carried out during development has a profound effect on the viability of mouse offspring, but does not have this detrimental effect when carried out in adulthood (Muglia et al. 1995). For instance, mice with CRF genetically removed during adulthood show a blunted, but still intact stress response (Jacobson et al. 2000; Weninger et al. 1999).

Two independent lines of CRF_1 receptor knockout mice have been produced and both displayed decreased anxiety across several tests (Smith et al. 1998; Timpl et al. 1998). Interestingly, the decrease in anxiety following CRF_1 receptor knockout was also seen in a line of mice that have the CRF_1 receptor knockout restricted to the forebrain (Muller et al. 2003). These mice have a lack of CRF_1 receptors in limbic areas of the brain but still express these receptors in the pituitary. Because of this, measures of basal HPA axis activity are normal, but altered anxiety behaviours can still be detected. This is an important piece of evidence for the role of centrally acting CRF in mood in addition to its role in regulating corticosteroid release.

In contrast to the findings with CRF_1 receptor mutants, CRF_2 receptor knockout mice showed increased anxiety (Bale et al. 2000; Kishimoto et al. 2000; but see also Coste et al. 2000) as well as increased immobility in the forced swim test

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3.4 BDNF

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(Bale and Vale 2003). This adds to the evidence that CRF_1 and CRF_2 receptors have broadly opposing roles in mediating emotional behaviour.

Further to this, weight and food intake were investigated in these mice. Body weight was not found to differ, and food intake was not altered at baseline. Following 24 h of food deprivation, however, CRF_2 receptor knockout mice were found to eat less than wild-type mice despite there still being no detectable difference in body weight (Bale et al. 2000). This may relate to the changes in feeding behaviour seen during a depressive episode, but are only noticeable after a mild stressor such as acute food deprivation is applied.

Receptors for the corticosteroids that are the product of HPA axis activity are also expressed centrally. Mineralocorticoid receptors have high affinity for corticosteroids, and several studies using mutant mice have helped in investigating the function of these receptors. Global knockout of these receptors proved to be perinatally lethal as corticosteroid signalling is vital to early lung development (Cole et al. 1995). Forebrain-specific deletion of mineralocorticoid receptors, however, produced viable offspring. These mice showed increased immobility in the forced swim and tail suspension tests (Boyle et al. 2005). However, overexpression of these receptors was also shown to result in increased immobility in the forced swim test, as well as increased anxiety-like behaviour in the elevated plus maze (Wei et al. 2004). This suggests an inverted U relationship between central corticosteroid signalling and emotionality.

The use of mutant mice has therefore shed some light on the roles of the CRF system in depression-related behaviours, and provided strong evidence for a key role for centrally expressed CRF receptors. This consideration of the wider CRF system and beyond the HPA axis has further avenues to be explored using mutant mice. For example, the testing of urocortin mutant mouse constructs in tests of depressive-like behaviour have begun (e.g., Chen et al. 2006; Neufeld-Cohen et al. 2010) although an extensive literature in this area is awaited. These models may provide further information on subtle but life-long changes to the CRF system.

3.4 BDNF

Recent theories regarding the mechanisms of depression and antidepressant action go beyond the role of neurotransmitter systems to emphasise the importance of neurotrophins (Hashimoto 2010). Trophic factors, such as BDNF, are integral to neuronal development and survival as well as neuroplasticity not only during early life but also in adulthood (Thoenen 1995). Moreover, expression of BDNF in the adult rodent brain was found to be reduced by corticosteroids and stress, and increased by antidepressants (Dwivedi et al. 2006). These findings and many others make BDNF an attractive addition to a unified neurobiological understanding of depression.

BDNF knockout mice were first produced in 1994 and found to have a plethora of detrimental phenotypes as well as perinatal lethality (Ernfors et al. 1994).

Behavioural work has therefore focused on heterozygote BDNF knockout mice. These mice, conversely, show relatively normal baseline behaviours including unaltered performance on the elevated plus maze and normal sucrose consumption (MacQueen et al. 2001). The mice also showed no change (MacQueen et al. 2001) or only subtle effects (Chourbaji et al. 2004) in various forms of the forced swim test. Overexpression of BDNF, however, was found to result in an antidepressant-like phenotype in the forced swim test, but also increased anxiety in the elevated plus maze (Govindarajan et al. 2006).

Conditional knockout mice that either have life-long or only adult reductions of BDNF have also been produced (Chan et al. 2006), allowing the dissection of the consequences of BDNF depletion during development from those during adulthood. The findings in these lines were surprisingly similar, with both showing a depressive-like phenotype in the tail suspension test but an antidepressant phenotype in a three exposure forced swim test paradigm (Chan et al. 2006). Neither line demonstrated changes in the elevated plus maze. These similarities between the two lines suggest that reductions in BDNF post-development are sufficient to produce the phenotypes, although once again, this phenotype is not consistently depressive-like.

Indeed, the role of BDNF in the pathogenesis of depression has been questioned (Groves 2007), although the case for a role of BDNF in antidepressant activity seems strong. The latter is supported by evidence that each of BDNF heterozygote mice, inducible BDNF knockout mice, and mice expressing non-functional versions of trkB, the high affinity receptor for BDNF, are resistance to the effects of antidepressant treatment in the forced swim test (Saarelainen et al. 2003; Adachi et al. 2008; Monteggia et al. 2007). It is worth noting that the baseline affective behaviours of the trkB mouse line are normal (Saarelainen et al. 2003; Zorner et al. 2003).

Overall, whilst the importance of BDNF in emotionality is still under investigation, current data suggest that at least in the hippocampus, BDNF gene expression is decreased by stress and corticosteroids and increased by antidepressant treatment. However, whilst data from genetically altered mice indicate that antidepressant effects require BDNF signalling, there does not appear to be such a strong link between BDNF signalling and depressive-like behaviours.

4 Concerns and Considerations

4.1 Background Strain

The issue of background strain has already been raised in this chapter, particularly in relation to the phenotype of 5-HT transporter knockout mice that differs across several lines. This is addressed and discussed extensively in Holmes et al. (2003a). The simplest explanation for the differences is that the various wild-type mice used

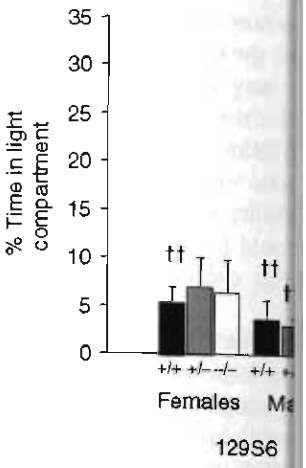

Fig. 3 Percentage of time spent in the light co box for wild type and 5-HT transporter knocko All mice on a 129S6 background spent very li dark box. In comparison, wild-type mice on a C in the light compartment than their wild type 12 anxiety phenotype of the 5-HT transporter kn et al. (2003a)

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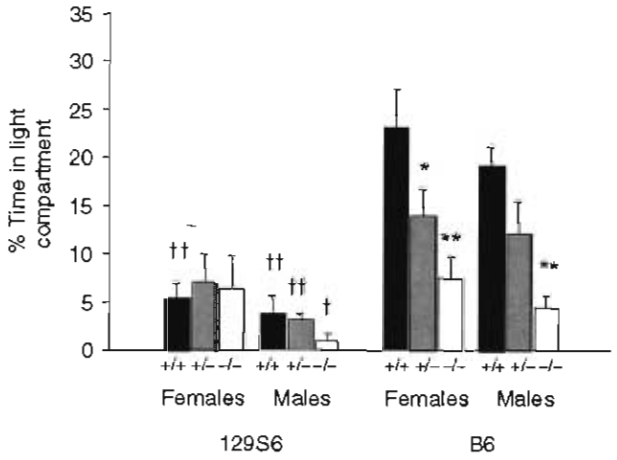

Fig. 3 Percentage of time spent in the light compartment of a 10 min exposure to the light/dark box for wild type and 5-HT transporter knockout miee on either a 129S6 or C57Bl/6 background. All mice on a 129S6 background spent very little time in the light, anxiogenic area of the light/dark box. In comparison, wild-type mice on a C57Bl/6 background spent a greater amount of time in the light compartment than their wild type 129S6 counterparts. The latter difference enables the anxiety phenotype of the 5-HT transporter knockout mice to be detected. Taken from Holmes et al. (2003a)

to generate the mutants do not provide a sufficiently sensitive baseline to detect differences. For instance, Holmes et al. (2003a) compare 5-HT transporter knockout mice on two different background strains, 129S6 and C57Bl/6, in the light/dark box (see Fig. 3). In this test, a decrease in time spent in the light compartment would reflect a high-anxiety phenotype. As can be seen, however, the 129S6 wild-type mice spend very little time in the light compartment, making a further decrease difficult to observe. In contrast, the C57Bl/6 wild-type mice spend more time in the light compartment, therefore giving a baseline from which a decrease can be observed. The behaviour of wild-type control mice, therefore, can affect the sensitivity of the tests. Further discussion of this issue can be found in Jacobson and Cryan (2007).

Another theory to explain the lack of consistent phenotype across different 5-HT transporter knockout lines is that genes flanking the mutant construct are incorporated into the genome of experimental mice during backcrossing onto a new background strain. In the case of the Holmes et al. (2003a) study, this would result in "129 genes" being inserted into C57Bl/6 mice. The observed decrease in time spent in the light compartment of the light/dark box may therefore be due to these flanking genes being inserted into the mutant mice and not because of loss of the 5-HT transporter gene *per se*. Sequencing of the site of insertion would reveal the likelihood of this confound.

Finally, genes that modify the effects of the mutant construct may exist at sites distal to its insertion, and these genes may only be present in particular background

strains. For instance, one background strain may carry a particular allele of a gene that can compensate at a molecular level for the loss of the 5-HT transporter gene, whereas a different non-modifying allele may be present in other background strains. In this case, a possible explanation for the difference in phenotype between 5-HT transporter knockout mice on the C57Bl/6 background and that on a 129S6 background may be due to a protective genetic variant at another site present in the latter but not the former mice. This possibility would require extensive investigation as the putative genetic difference could be located anywhere in the entire genome. Further discussion of these theories can be found in the Holmes et al. (2003a) paper.

The controversy surrounding links between the 5-HT transporter and emotionality may be an example of how these issues also apply to human studies. When dealing with human subjects, there is a high degree of genetic heterogeneity. By genotyping for only one gene and then linking this to complex behavioural traits ignores the possibility that other genes may contribute, not only to the behaviour in question, but also to the expression level of the protein encoded by the gene in question. These gene × gene interactions may account for some of the "missing heritability" not yet accounted for by known genetic risk factors for various psychiatric conditions. While in vivo assessments of functional protein levels in humans can be expensive or impractical, histological measures of protein expression in experimental animals provide a way of ensuring that the genetic manipulation performed has the expected effects at a molecular level. While this may not always explain discrepancies in results, it is a useful validation step in using and producing mutant mouse lines.

4.2 Sex Effects

It is well established that females are more likely to develop clinical depression than males (DSM IV-TR; Weissman and Klerman 1977), a striking vulnerability difference for which the underlying mechanism is not yet known. In this regard, it would be valuable to recapitulate such sex difference in experimental animal models, but this is complicated by evidence that male mice and rats are more susceptible to learned helplessness than females (Caldarone et al. 2000; Steenbergen et al. 1990). This suggests that contrary to findings in humans, in rodents males are more predisposed to developing depressive-like phenotypes than females. What should be expected in terms of sexual dimorphism in depressive-like behaviours in mutant mice is therefore unclear.

As in the case of the baseline behaviour of mice with different background strains, male and female mice provide different baselines on a variety of behaviours. Thus, only investigating one sex may mask effects that would otherwise be apparent in the other. If striking differences are found following genetic manipulation, it may be that sex hormones are modulating the effects seen, in which case providing a further of avenue of study that could be highly translatable. Many

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4.4 The Perfect Model?

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basic studies with mutant mice use only males to avoid having to control for variation in the oestrus cycle during behavioural testing. Nevertheless, since sex hormones may impact on phenotypic differences between mutant and wild-type mice, investigations using both male and female mice could add further insight into the role that sex differences play in depression vulnerability.

4.3 Environmental Factors

As in humans, there is considerable evidence from animal studies that adverse life events such as stress, including that experienced during early life, increase depression vulnerability (e.g. Willner 2005; see chapter in this volume by Harro). Moreover, it seems highly likely that genetic and environmental risk factors interact in ways that are not yet fully understood to increase predisposition to depression (e.g., Kendler et al. 2001). A potentially powerful way to investigate this is through the combination of genetic and well-controlled environmental manipulations in mice. There are increasing examples of such studies emerging in the literature, which are reviewed elsewhere.

4.4 The Perfect Model?

So what can we hope for in attempting to model depression using mutant mice, and are we there yet?

Depression is a complex condition consisting of a variety of symptoms, only a small number of which are possible to investigate in rodents. However, as noted in this chapter, there are some core behavioural symptoms that are accessible to investigation in rodents in a highly relevant way, and these can be expanded to include measurement of physiological changes such as the sleep/wake cycles and food intake. Nonetheless, in the case of genetic mouse models of depression the majority of studies being reported at present often rely heavily on measures of behavioural despair such as the forced swim test and tail suspension test without exploring the wider symptomatology of depression. Often a more complex analysis of the current models would give greater insight into their validity. Hopefully, this will be a feature of future models.

While a genetic mouse model that recapitulates the fullness of the symptoms that typically feature in a clinical depressive episode seems overoptimistic and probably unachievable, a frank assessment of a wider variety of behaviours than is typically presented in the current literature may provide a clearer view of the likely contribution to depression pathophysiology of specific genes. Nevertheless, given that specific genes, and often genes with unclear functions, can be manipulated in an increasingly powerful and controlled way, key questions can now be asked about the contributions of a single gene to a specific behavioural processes that are

highly relevant to depression vulnerability, in a way that is not possible in human gene association studies. This is not to deny, however, sometimes confounding effects that can be occur from targeting genes in mice, such as noted above with the example of the 5-HT transporter.

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