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Genetic animal models of depression

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Abstract

Depression, as part of a larger class of affective disorders, is one of the world's most deleterious and widespread neurobehavioral diseases. However, much remains to be discovered concerning depression, due to the daunting complexity of its pathological mechanism and etiology. Various animal models have been proposed over the years, some of which have come into wide use, particularly in the area of pharmacological screening. By combining behavioral and physiological analyses with mutant and transgenic animal models, researchers are able to determine the role of specific genes and proteins in the pathogenesis of depression. Discussing several behavioral and transgenic/mutant rodent models, this chapter briefly summarizes current progress in this area of psychiatric research.

Introduction

Affective disorders have continued in recent years to take an alarming toll on populations across the globe. Depression is a common disease, symptoms of which may include chronic fatigue, irritability, erratic patterns of sleep and appetite, anhedonia, weakened ability to concentrate, constant feelings of guilt, and thoughts of suicide (Nestler et al 2002). Depression is widespread across different age and social groups, and is in part genetically determined (Levinson 2006; Zimmermann et al 2008). Twice as prevalent in women as in men, major depressive disorder has a lifetime prevalence of between 10% and 20% across genders (Heurteaux et al 2006; Levinson 2006). The apparent complexity of the disease, in part due to its high rate of comorbidity with other affective disorders, such as obsessive-compulsive disorder and generalized anxiety disorder, has presented a challenge to clinical research in defining and isolating molecular substrates specific to depression (Zitterl et al 2000).

While the underlying pathological mechanisms of depression remain unclear, the necessity for this knowledge becomes increasingly evident. Certain concepts, such as the monoamine theory of depression, have produced drug treatments that are highly effective in some patients. Serotonin, norepinephrine, and dopamine have been identified as the key mediators in antidepressant action (Urani et al 2005). Tricyclic antidepressants (e.g. imipramine) as well as selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and sertraline are known to act directly on monoamine pathways. Paralleling clinical data, these and similar compounds have also proven efficacious in alleviating depressive-like behaviors in animal models (Bessa et al 2009).

Beyond the monoamines, several other mediating biological systems have been identified in the pathogenesis of depression, including the hypothalamic-pituitary-adrenal (HPA) axis and

neurotrophins, such as brain-derived neurotrophic factor (BDNF) (Levinson 2006). For example, reduced expression of BDNF in the hippocampus has been linked to some symptoms of depression (Racagni and Popoli 2008). Additionally, antidepressant drug treatment has been shown to induce the up-regulation of hippocampal BDNF. Similarly, direct infusion of BDNF or neurotrophin 3 to the dentate gyrus has also been demonstrated to produce an antidepressant effect in rodent models (Shirayama et al 2002). BDNF production is regulated by serotonin; however, the presence of BDNF in turn modulates this neurotransmitter by increasing expression of tryptophan hydroxylase, the rate-limiting enzyme in serotonin's biological synthesis (Martinowich and Lu 2008).

The serotonin transporter (SERT) is a common target of many antidepressant medications, especially SSRIs. Manipulation of SERT function has proven highly efficacious in the treatment of depression as well as several other mood disorders (Canli and Lesch 2007). Other treatments may target dopamine (DA) or norepinephrine (NE) transporters, either selectively or in addition to SERT, as these proteins are also implicated in depressive disorders (Perona et al 2008). In addition to monoaminergic action, norepinephrine reuptake inhibitors (NRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) also modulate the expression of brain neurotrophins, contributing to their therapeutic effects.

The hypothalamic-pituitary-adrenal (HPA) axis is another system commonly implicated in depression pathogenesis. This endocrine pathway is central to stress response across a wide variety of species, and its hyperactivation is a common biomarker of chronic stress and anxiety. Under conditions of acute stress, the hypothalamus produces corticotrophin releasing factor (CRF), which in turn stimulates the production and release of adrenocorticotrophic hormone (ACTH), from the anterior pituitary. ACTH induces the release of cortisol, a stress hormone, which has been consistently shown

to be elevated in depressed individuals. Since effective treatment with antidepressants normalizes a patient's plasma cortisol levels, drugs have been developed to target corticosteroid receptors crucial for the regulation of the HPA axis (Urani, Chourbaji et al. 2005).

More recently, some focus has been placed on the possible epigenetic etiology of depression through modification of histones and DNA (Tsankova et al 2007). For example, DNA cytosine methylation, developed as a result of stress during infancy and pre-adolescence, may have a role to play in depressive symptoms experienced by adults. It is likely that methylation in promoter regions may act to reduce expression of signaling proteins, thereby inducing a depressive-like state in animals. This epigenetic response to stress in the early period after birth may be linked to depression exhibited later in life. In addition, the effects of certain antidepressant drugs have been linked to nucleic acid histone acetylation, which may reverse this process, in effect increasing translation of these same proteins (Tsankova et al 2007). Recent studies have shown increased methylation surrounding specific gene regions in mice receiving poor maternal attention (licking) as pups, also leading to their higher depressive-like phenotype. Interestingly, acetylation of histones in the same regions has been shown to alleviate these symptoms in some cases (Nestler et al 2002).

Experimental Models of Depression

Animal models are widely employed in the study of neurobiological mechanisms of depression (Geyer and Markou 1995; Kalueff et al 2008; Kalueff and Murphy 2007). Ideal models for depression must be reasonably analogous to the human disease, allow for objective monitoring, be reversible through similar treatment modalities, and be reproducible between laboratories (Cryan et al 2002; Cryan and Slattery 2007; Frazer and Morilak 2005). Although some of the more complex symptoms of depression may be difficult to induce in animals, a number of models exhibit considerable construct validity in targeting other clinical

endophenotypes of depression (Cryan and Mombereau 2004; Cryan and Slattery 2007; Willner 1997). Antidepressant treatment has been shown to affect behavioral responses in these models, indicating that certain depression modeling paradigms are pharmacologically sensitive, and can therefore be utilized in the testing of antidepressant drugs in mice.

A clear distinction must be made between animal models of depression and animal tests (or screens) of antidepressant drugs. A model attempts to reproduce some element of pathology seen in another species, and therefore is reliant on high construct validity. In contrast, a screen places greater focus on predictive validity and may not bear any specific resemblance to a known disease or disorder. Each type of animal paradigm is equally important to progress in biological psychiatry and drug discovery. Additionally, automated versions of some of these tests are currently available (Crowley et al 2004; Juszcak et al 2006), enabling consistent behavioral measurement, standardization of experimental protocols, and increased throughput in testing.

Coat state assessment is a fast and simple qualitative method for assessing depression-like states in mice through observation of the condition of an animal's fur. In rodents, coat state tends to decline with increased depression, similar to poor hygiene frequently observed in depressed human patients (Piato et al 2008; Yalcin et al 2005; Yalcin et al 2007). Antidepressants have been shown to improve grooming behavior and coat condition in mice while reducing depression-like symptoms (Piato et al 2008; Yalcin et al 2005; Yalcin et al 2007). Coat condition in individual body regions can be scored with either a 1, indicating dirty or disheveled fur, or a 0, to indicate a well-kept coat and normal grooming.

Sucrose consumption is another useful paradigm based on anhedonia, one of the core symptoms of depression, manifest in a decreased interest in pleasurable activities (Cryan and Holmes 2005). There are several commonly used tests to assess hedonic deficits in mice. The

sucrose consumption test examines anhedonia in a relatively short period of time without the need for expensive equipment or extensive training of the test animals. In this model, a mouse is given a free choice between regular tap drinking water and a 1-4% sucrose solution. Usually, mice show a clear preference for the sweetened water, while depressed animals demonstrate markedly less interest. Pure chance would theoretically result in animals drinking equally (50%) from each bottle, and a preference for sucrose of less than 65% is considered to be an indication of hedonic deficits (Strekalova et al 2004). As various antidepressant drugs can reverse the anhedonia-like reduction in preference for sucrose (e.g., (Jayatissa et al 2008; Xu et al 2008; Zhao et al 2008)), this test is widely used in the screening of antidepressant drugs.

Although it does not induce experimental depression in mice, the forced swim test (FST) is one of the most commonly utilized ethological models for fast high-throughput antidepressant screening. The FST places mice in an inescapable aversive situation and measures learned helplessness by an increased duration of immobility in the water. Animals are placed in an enclosed water container and observed for 6 min, assessing the total duration of immobility throughout the swimming trial. Rodent FST has high predictive validity and is widely used in research investigating the efficacy of antidepressant drugs (Bai et al 2001; Bourin et al 2005; Burne et al 2006; Hunsberger et al 2007; Strekalova et al 2004).

In the tail suspension test (TST), each mouse is suspended in a hanging position by the mid-section of its tail. Subjects initially engage in vigorous escape behaviors, but eventually succumb to immobility. As in the FST, longer durations of TST immobility directly indicate a heightened degree of despair. Due to its ability to measure this change in affective phenotypes, the TST has become a commonly used screening method for antidepressant properties of drugs.

Antidepressant drugs generally decrease the duration of TST immobility in mice (Bai et al 2001; Bourin et al 2005; Hunsberger et al 2007; Juszczak et al 2006).

Chronic unpredicted mild stress (CUMS) presents mice with a random sequence of stressors to induce (rather than simply measure) a depressed state. CUMS brings about a reduced preference for sucrose or saccharin intake in mice, a symptom of anhedonia (see above). CUMS has considerable face validity as an ethological model of depression, as this model can cause several symptoms of depression: decreases in sexual and aggressive behavior, changes in sleeping habits, loss of body weight, pituitary-adrenal hyperactivity, an increased threshold for brain stimulation reward, and an abolishment of place conditioning. These behavioral deficits can be reversed through chronic treatment with antidepressants, emphasizing the pharmacological sensitivity of the CUMS model (Harkin et al 2002; Pothion et al 2004; Willner 1997; Willner et al 1996).

Genetic Animal Models of Depression

Genetically modified animals are currently in wide use as models for human brain pathologies, including depression and anxiety (El Yacoubi and Vaugeois 2007; Gould and Einat 2007). As recent data has strongly linked clinical depression to genetic factors (Gordon and Hen 2004), researchers now focus on depression-related loci in both animals and humans in order to expand our understanding of the genetic basis of depression. Advanced techniques in molecular genetics have allowed for increasingly specific manipulation of gene expression in animals. The development and refinement of molecular methods for genetic modification, combined with previously established experimental models for the assessment of depression-related behaviors in animals, can further enhance our comprehension of the genetic factors underlying depression

As mentioned above, there are a number of available experimental models that have shown high validity for assessing anxiety and depression-like behavior in animals. The power of a given genetic model is mediated by the specificity of the model, the depth of an experimenter's knowledge of secondary effects, and the nature of the question being evaluated (Gordon and Hen 2004). The following section provides examples of studies that have utilized genetic techniques to alter depression phenotypes and develop improved treatments for depression-related disorders.

Generation of Knockout Mice

The conventional knockout generation technique has led to the development of numerous mutant strains which have advanced our understanding of affective disorders. The process typically begins by localizing an 80- to 100-kb genomic fragment from the genomic library of a known mouse strain (e.g., 129/SvJ, C57BL/6J) by employing PCR primers which are generated specifically to sequence within a gene coding region lacking an intron. Once a gene of interest has been selected and isolated, it is then inserted into a short, easily manipulated fragment of DNA, referred to as a vector. The vector containing the genomic insertion is then further modified to inactivate the original target gene. This is accomplished by the insertion of another marker sequence that makes the cells resistant to specific antibiotics. The vector, containing the inactivated gene of interest, is transferred into mouse embryonic stem (ES) cells.

The embryonic stem cells are then cultured and grown in an antibiotic-containing medium. This method ensures that only cells that have incorporated the inactive sequence of the target gene will survive. Once enough of these cells have been isolated they are then injected into early mouse embryos and transferred into surrogate mothers and allowed to develop normally. The resulting pups, referred to as chimeras, contain the active (+) version of the target gene in some cells and the inactive (-) version in other cells. These chimera mice are then mated with normal

mice. Pups from the resulting litter are then genotyped to determine which carry each variant of the target gene. About 25% of the pups from this litter will have inherited the (-) gene from both parent mice and are classified as knockout mice. These mice completely lack the active form of the gene in all cells and are referred to as global knockouts.

Another method for developing knockout models allows for greater specificity with regard to where and when the gene inactivation occurs. This method, called the Cre-lox site-specific DNA recombination system, is another extremely useful genetic tool for addressing a large range of biological questions (Sauer 1998). The Cre-lox system can be designed to target the expression or ablation of any gene for which the basic molecular information is available, specific to any tissue or time in development allowing for more deliberate manipulation than conventional methods. This system is employed for the genetic manipulation of embryonic stem cells. The Cre-lox system has a wide scope of uses, including the design of conditional mutations, the ability to precisely dictate chromosome rearrangements, removal of unwanted DNA sequences, and targeted DNA integration. It has been particularly useful in the design of genetically modified mice, with respect to the generation of more sophisticated mouse models of human disease and for allowing a more precise understanding of gene function in animals.

The advancement of modern molecular techniques and the application of these techniques to the creation of knockout mice demonstrate the benefits of the capacity to target and limit gene expression or absence in regions of interest. Furthermore, this allows for the testing of very specific hypotheses that would be otherwise impossible to study through the traditional pharmacological and neurobiological methods. These same traditional tools, however, when used in conjunction with genetic techniques, allow for a more comprehensive and systems-based

understanding of animal depression-like behavioral phenotypes and may lead to improved treatment for human pathogenesis.

Examples of depression-like phenotypes

While all of the mutant and transgenic mice developed for depression research exhibit behaviors classifiable on the depression spectrum, each specific model exhibits distinguishable differences in behavioral phenotype. One interesting genetic mouse model in current use for the study of depression-related behavior is the interleukin-6 (IL-6) knockout (-/-) mouse strain. The study of cytokine-dependent mechanisms is of particular importance as they have been implicated in the pathogenesis of depression. Specifically, the up-regulation of IL-6 has been observed in patients exhibiting clinical signs of depression, whereas IL-6 is subsequently down-regulated following the administration of antidepressants (Chourbaji et al 2006). IL-6 (-/-) mice have shown resistance to models of induced depressive-like phenotype and learned helplessness. This strain also exhibits a decrease in anhedonia and shows reduced immobility in FST and TST. Based on these observations, IL-6 -/- mice may represent a valuable tool to study molecular and genetic mechanisms of cytokine-dependent depression-like behaviors.

Another mutant strain of interest is the TWIK-1-related K⁺ channel knockout mouse (TREK-1) (Heurteaux et al 2006). This study demonstrates that specific deletion of this channel protein confers to these mice a resistance to experimentally modeled depression as measured by increased mobility in the FST and TST, as well as reduced levels of corticosterone compared to wild-type mice after exposure to stress (Heurteaux et al 2006). Additionally, TREK-1 knockout mice have significantly higher serotonergic neuronal activity compared to wild-type controls. This was a unique discovery in that it was the first to specifically implicate an ion channel in depression-like animal behavior.

Several mouse strains featuring transgenic or mutated glucocorticoid receptor genes have been tested for potential in modeling depression. Among the strains that have been modified and studied are GR^{+/-} and YGR (Ridder et al 2005; Tronche et al 1998).

The GR^{+/-} mouse, which has only one functional allele for the glucocorticoid receptor, exhibits a significantly increased disposition for learned helplessness in the chronic mild stress paradigm (Chourbaji et al 2005; Ridder et al 2005), despite that they are phenotypically similar to wild-type mice in other behavioral tests for depression-like response. GR^{+/-} mice also respond to acute stress with unusually high corticosterone levels as compared to controls. The YGR transgenic strain, which has been modified to over-express the same glucocorticoid receptor, exhibits a behavioral and physiological phenotype nearly opposite that of the GR^{+/-} mouse. YGR mice have been shown to possess an enhanced resistance to stress, both in reduced helplessness behavior and diminished corticosterone response, neatly confirming the role of this receptor in depression-like animal behavior (Reichardt et al 2000).

Neuropeptide Y (NPY) has been shown to reduce anxiety- and depression-like behaviors in rodents when its action is mediated by Y1 receptors, whereas the action of NPY on Y2 receptors has the opposite effect (Painsipp et al 2008). There are also a number of other receptor subtypes on which NPY can act. The utilization of specific NPY receptor type knockout or knockdown mice is thus a promising area of research. Specifically, Y2^{-/-} and Y4^{-/-} mice are being used extensively in anxiety and depression-related research paradigms. When assessed in the standard measures of rodent anxiety and depression (open field, elevated plus maze, stress-induced hyperthermia and TST) these knockout mice exhibit reduced anxiety-related behavior and enhanced locomotor activity (reduced depressive-like behavior) relative to their wild-type littermates (Painsipp et al 2008).

Conclusion

The use of translational genetic animal models has clearly proven a potential to significantly improve our understanding of psychiatric pathogenesis. The ability to target specific genes or systems of interest through knockout, under-expression or over-expression allows researchers to examine specific mechanisms in relation to behavioral phenotypes. Utilizing these approaches, researchers have and will continue to make remarkable progress toward a better understanding of the mechanisms and systems involved in depression spectrum disorders. For these reasons, genetic animal models are of utmost importance in the collective scientific effort to isolate and quantify specific elements of brain disorders and to propose superior models to more accurately represent the complexity and multi-faceted nature of human affective pathogenesis. By working toward models that will provide greater predictive validity and higher reliability, we can increase the rate at which novel drug therapies can be proposed and discovered. The tools of molecular genetics will allow this predictive power to be combined with a better representation of the specific molecular action involved in both disease and therapy.

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