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Animal models of depression and anxiety: What do they tell us about human condition?

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ABSTRACT

While modern neurobiology methods are necessary they are not sufficient to elucidate etiology and pathophysiology of affective disorders and develop new treatments. Achievement of these goals is contingent on applying cutting edge methods on appropriate disease models. In this review, the authors present four rodent models with good face-, construct-, and predictive-validity: the Flinders Sensitive rat line (FSL); the genetically "anxious" High Anxiety-like Behavior (HAB) line; the serotonin transporter knockout 5-HTT$^{-/-}$ rat and mouse lines; and the post-traumatic stress disorder (PTSD) model induced by exposure to predator scent, that they have employed to investigate the nature of depression and anxiety.

1. Introduction

Advances in cellular and molecular biology and imaging have led to identification of receptor changes, neuropeptide systems alterations, dysregulations in intracellular signaling, changes in gene sequence or expression, and alterations in brain circuits that may be relevant to the pathophysiology of affective disorders as well as to the mode of action of therapeutic drugs. Although studies of healthy human subjects and animals using the advancing modern technologies enhance our basic knowledge, elucidation of disease etiology and pathophysiology as well as development of new treatments, is contingent on availability of appropriate disease models.

Unipolar depression and bipolar disease constitute a major public health problem due to the pain and anguish they cause in innumerable afflicted individuals and are a heavy burden to society. The hypotheses of dysregulated serotonergic and noradrenergic system function as etiologic agents of the disorder have dominated the field for decades, and the currently marketed antidepressants act by modulating these two systems (and to a lesser extent the dopaminergic system), despite a substantial number of non-responder patients (Thase and Rush, 1995). Thus, there exists a major unmet medical need, the resolution of which is contingent on elucidating the disease etiology and pathogenesis. Two

Abbreviations: 5-HT, serotonin; 5HT$_{1A}$, serotonin 1A receptor; 5-HTT, serotonin transporter; 5-HTTLPR, serotonin transporter-linked polymorphic region; 8-OH-DPAT, 8-hydroxy-2-(dipropylamino)tetralin hydrobromide, 5-HT$_{1A}$ receptor agonist; AC, anterior cortex; AVP, arginine vasopressin; BDNF, brain-derived neurotrophic factor; BIBP3226, N-[(1R)]-4-[(Aminoiminomethyl)amino-1-[[[(4-hydroxyphenyl) methyl] amino]carbonyl]butyl-α-phenylbenzeneacetamide trifluoroacetate; BrdU, Bromodeoxyuridine; BrdU-IR, Bromodeoxyuridine immunoreactive; CBC, cut-off behavioral criteria; cNOS, constitutive nitric oxide synthase; CRH, corticotropin releasing xhormone; DEX/CRH, dexamethasone/CRH test; DFP, diisopropylfluorophosphate; DOI, R(−)-2,5-dimethoxy-4-iodoamphetamine, 5-HT$_{2A/C}$ receptor agonist; EBR, extreme behavioral response; ECT, electroconvulsive therapy; EPM, elevated plus maze; EPM, elevated plus maze test; fMRI, functional magnetic resonance imaging; FRL, Flinders Resistant Line; FSL, Flinders Sensitive rat line; FST, forced swim test; HAB, High Anxiety-like Behavior; HPA, hypothalamic–pituitary adrenal; IR, immunoreactive; LAB, low anxiety-related behavior; MBR, minimal behavioral response; nNOS, neuronal nitric oxide synthase; NPS, neuropeptide S; NPY, neuropeptide Y; OCD, obsessive compulsive disorder; PAG, periaqueductal gray; PBR, partial behavioral response; PSS, predator scent stressor; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus; REM, rapid eye movement; SNP, single nucleotide polymorphism; SSRI, selective serotonin reuptake inhibitor.

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factors have played a cardinal role to bring about this situation: (1) the fact that the phenotype, exhibiting a range of symptoms, likely represents several pathologies. This is reflected in the changing classification systems over the years, perhaps the most controversial being whether melancholia is a separate entity, distinct from other depressions and how different is the neurobiology of unipolar from bipolar depression. Thus, it is *a priori* not feasible to create a model that will simulate the symptoms and deranged pathologies in a comprehensive way as *a priori*, and (2) the paucity of adequate animal models is, in part, a consequence of the nature of the disease(s) and their classification.

Three general strategies to develop animal models have been used: genetic manipulation, selective breeding for extremes in a particular behavioral phenotype, and environmental manipulations. In addition, combination of these strategies, that is superposing environmental influences on genetically-modified or selectively-bred animals is employed. Regardless of the approach used, the basic criteria to be fulfilled for a satisfactory model are face, predictive and construct validity. Briefly, i. face validity indicates that the phenotype of the model is similar to the human syndrome it is supposed to imitate; ii. predictive validity stipulates that a manipulation known to influence human pathology (in a deleterious or positive way) will have comparable effects in the animal model, e.g., exposure of the animal model to stressful events, enhanced care/enriched environment or administration of antidepressants/mood stabilizers, will result in similar consequences as observed in human subjects following the same exposure; and iii. construct validity, to which face and predictive validity contributes, presupposes that a human disease and the animal model share common pathological substrates that can explain pathology in both, thereby enabling generation of a common mechanistic theory and experimental testing of the most salient clinical aspects of a given disease (see Table 1).

This review focuses on four rodent (rat) models: rats of the genetically "depressed", Flinders Sensitive Line (FSL); the genetically "anxious", High Anxiety-like Behavior (HAB) rat breeding line;

Table 1
Summary table depicting the validity of the animal models discussed within the review. n/a not assessed.

	Patients	FSL rats	HAB rats	5HTT$^{-/-}$ rodents	PTSD model
Face validity (symptomatology)					
Activity	Psychomotor retardation	Reduced bar pressing for rewards	Reduced (EPM, LDB)	Reduced (EPM, open field)	Reduced (EPM) only in the affected animals (EBR)
Passive stress coping	Yes	Yes (increased immobility FST)	Yes (increased immobility FST)	Yes (increased immobility FST)	Yes (only in EBR rats)
Anxiety	Often increased	No anxiety	High anxiety (selection criteria)	Increased anxiety	High anxiety (in EBR and PBR rats)
Anhedonia	Yes	Yes (following stress)	Yes (lower sucrose preference)	Yes (lower sucrose preference)	Yes (lower sucrose preference) (only in EBR rats)
Appetite	Reduced	Reduced	Unknown	Increased (only in females)	No
Weight	Weight loss	Lower body weight	Lower body weight	Lower body weight (females)	No
Cognitive performance	Reduced	Yes/no (dependent on test)	n/a	Altered (depends on test)	Yes — only in tasks associated with the memory of the stress (only in EBR rats)
Social behavior	Often abnormal	Enhanced affective aggression	Altered (aggression, social interaction, maternal)	Reduced (aggression, sexual behavior, social play, social interaction)	Reduced (sexual behavior, social interaction) and enhanced (aggression) (only in EBR rats)
REM sleep	Elevated	Elevated	Reduced	n/a	n/a
HPA axis dysregulation	Yes	Yes	yes	Yes	Yes (in EBR and PBR rats)
Cardiovascular morbidity	Increased	Increased	n/a	No	Increased (only in EBR rats)
Monoamine dysregulation	Suggested	Altered	Altered	Altered	n/a
Amygdalar responsiveness	Increased	n/a	Increased	Increased	Increased (only in EBR rats)
Pain perception	Altered	Probably altered	Altered	Altered	Altered
Predictive validity (treatment)					
Tricyclic antidepressants	Effective	Effective	Effective	n/a	n/a
Selective serotonin-reuptake inhibitors	Effective	Effective	Effective	Not effective	Effective
Monoamine uptake inhibitors	Effective	Effective	n/a	Effective	n/a
Atypical antidepressants	Effective	Effective	n/a	n/a	n/a
Benzodiazepines	Effective	Effective	Effective	n/a	As treatment: effective As secondary prevention: increases vulnerability to subsequent stress
Etiological validity (causative conditions)					
Learned fearful associations	Increased (PTSD)	Increased	Increased (HAB)	Increased	Increased
Genetic predisposition	Suggested	Cholinergic sensitivity	AVP SNP (HAB)	5-HTT	Blunted HPA-axis response to stress — increased susceptibility to experimentally induced PTSD-like behavioral changes
Gene × environment interaction	Increased risk	Increased risk	Differential effects		Heritable factors involved only in part of the endophenotypes associated with the PTSD-like behavioral phenotype and influenced indirectly by interactions with environmental variables