A REVIEW

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A Review on animal models of depression

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Animal models in psychopharmacology are difficult to develop because of the convolution of the human mind and the inherent difficulty in stimulating a similar condition in laboratory animals. However, animal models in the psychopharmacology have contributed a lot to drug research. Depression is one among the most rampant forms of psychiatric disorders and a leading cause for morbidity and mortality. Since, the unexpected breakthrough of the first antidepressants the progress in developing more efficient medications has marked time, emphasizing the need to establish novel classes of antidepressants. Various animal models have been developed and are instrumental in detecting the antidepressant-like potential of novel compounds in preclinical settings. The models commonly used are diverse and were developed originally based on the behavioral consequences of stress, drug, lesion or genetic manipulations. The present review is an attempt to compile together various animal models employed for the screening of antidepressants.

Key words : Depression, Model, Animal, Antidepressants

Depression is a common, chronic, and potentially debilitating form of psychiatric disorders with a lifetime prevalence of about 15-20% (Kessler *et al*., 2005). According to World Health Organization, unipolar depression is projected to reach second place as leading contributor to the global burden of disease by the year 2020 (Murray and Lopez, 1997). As defined by the American Psychiatric Association (American Psychiatric Association, 1994), depression is a heterogeneous disorder often manifested with symptoms at the psychological, behavioral and physiological levels (Box 1).These symptoms are often recurrent and prone to become chronic, substantially interfering with an individual's ability to cope with everyday life. Depression is considered as a stress-related disorder underscoring the role of stress as a key determinant in disease etiology (Fava and Kendler, 2000). An estimated 40–50% of the risks for depression are genetically determined (Levinson, 2006). However; no single vulnerability gene has been identified yet, indicating a far more complex interplay of genetic and environmental factors underlying the causative etiology of this disorder (Nestler *et al*., 2002). It is exceedingly difficult to predict an animal model that perfectly recapitulates the symptoms of depression in human patients. Animals not only lack consciousness of self, self reflection and consideration of others but also hallmarks of the disorder such as depressed mood, low self-esteem or suicidality are hardly accessible in non-humans. However, depression, as other mental disorders, constitutes of intermediate or so-called endophenotypes that can be reproduced independently and evaluated in animals, including physiological, endocrinological and neuroanatomical alterations as well as behavioral traits (Box 2).

Box 1 : Symptoms of major depression (American Psychiatric Association, 1994)

- Depressed mood most of the day (in children and adolescents, irritability might signify a depressed mood)
- Markedly diminished interest or pleasure in all or most activities most of the day
- Large increase or decrease in appetite
- Insomnia or excessive sleeping
- Psychomotor agitation (evident by, for example, hand wringing) or slowness of movement
- Fatigue or loss of energy
- Indecisiveness or diminished ability to think or concentrate
- Feelings of worthlessness or excessive or inappropriate guilt
- Recurrent thoughts of death or suicide

Requirements for an animal depression model :

Nonetheless, numerous attempts have been made to create animal models of depression, or at least of the symptoms of depression, and criteria for their evaluation have been established. Some of the most widely cited criteria were developed by McKinney and Bunney around 40 years ago (McKinney and Bunney, 1969). They proposed that the minimal requirements for a valid animal

Box 2 : Depression-associated endophenotypes that can be modeled in mice and rat

Anhedonia

The loss of interest in pleasurable and rewarding actions is a core symptom of depression. Anhedonia in rodents can be assessed by the preference for a palatable reward such as sucrose solution or by intracranial self-stimulation.

Anxiety-related behavior

Anxiety is a symptom with high prevalence in depression. Therefore, animal models that are used to elucidate mechanisms underlying depression often display altered anxiety related behavior.

Neuroendocrine disturbances

Disturbances of the hypothalamic-pituitary-adrenocortical (HPA) axis are one of the most consistent symptoms in major depression. The functionality of the HPA axis can readily be assessed by challenge tests such as the dexamethasone suppression test or the combined dexamethasone/corticotropin-releasing hormone test.

Behavioral despair

Behavioral despair might be assessed with tests such as the forced swim test or the tail suspension test. Changes in appetite or weight gain. Depression in humans is often associated with large changes in appetite or weight gain, which is easily measured in rodents.

Alterations in sleep architecture

Disturbances in the circadian rhythm and especially in the sleep architecture are often observed in depressed patients. The sleep architecture, for example entry into rapid eye movement (REM) sleep in rodents, is accessible via electro-encephalogram (EEG)

Neuroanatomy

Depressed subjects display decreased hippocampal volume as demonstrated by magnetic resonance imaging. Rodents exposed to chronic stress or excess glucocorticoids exhibit similar signs of hippocampal loss of neurons and dendritic atrophy.

model of depression are:

- be reasonably analogous to the human disorder in its symptomatology (face validity),

- cause behavioral changes that can be monitored objectively,

- produce behavioral changes that are reversed by the same treatment modalities that are effective in humans (predictive validity) and

- should be reproducible between investigators. Originally, animal models of depression have been designed as screening tests to assess the efficacy of antidepressant drugs. These tests neglect the aspect of face validity but have a strong predictive validity regarding the identification of efficient antidepressant substances. Animal models of depression, in the proper meaning of the word, are expected to present with sufficient face validity and to shape the underlying disease etiology.

Animal models of depression :

Animal models are indispensable tools in the search to identify new antidepressant drugs and to provide insights into the neuropathology that underlies the idiopathic disease state of depression (Cryan *et al*., 2002). Various paradigms have been developed and are instrumental in detecting the antidepressant-like potential of novel compounds in preclinical settings. The models commonly used are diverse and were developed originally based on the behavioral consequences of stress, drug, lesion or genetic manipulation. As new targets are developed, both serendipitously and through hypothesis-driven research, existing animal paradigms are being modified and new tests are being developed to detect antidepressant actions of compounds acting on a broad range of neural and genetic targets (Cryan *et al*., 2002). The various animal models, used for the screening of antidepressants, are summarized in Table 1

Behavioral models :

The forced swim test **:**

The forced swim test (FST) was developed by Porsalt and colleagues in the rat and, subsequently in the mouse (Porsolt *et al*., 1977; Porsolt, 2000). This test is the most widely used tool for assessing antidepressant activity preclinically. The widespread use of this model is largely a result of its ease of use, reliability across laboratories and ability to detect a broad spectrum of antidepressant agents with no interaction with each other (Borsini and Meli, 1988). This model is based on the premise that, when rats or mice are forced to swim in an apparatus from where is no escape, they will, after initial frenzied attempts to escape, adapt a characteristic immobile posture and make no further attempts to escape. The movements made by the rodent are those necessary to keep its head above the water level. It is postulated that the immobility exhibited by the animal reflects a state of 'despair', resigning itself to the experimental situation. In a standard protocol, the rats are subjected two trials during which they are forced to swim as shown in Fig. 1 in a measuring flask (40 cm height x 18 cm in diameter) with water level of 15 cm (25 ± 2^0C), so that it cannot touch the bottom with its hind paws or tail, and climb over the edge of the apparatus. There is a 24 hr interval between the first and second trials; the first trial lasts 15 min, the second 5 min. the total duration (s) of immobility is measured during the second trial. The protocol is same in mice except that the vessel dimensions (20 cm height×

Table 1 : Summary of widely used depression models applicable in mice and rats

Animal model	Ease of use	Reliability	Comments	Reference
Behavioral				
Forced-swim test	High	High	High reproducibility; Sensitive to acute antidepressant treatments; does not reliably detect SSRIs	Porsolt *et al.*,1977; Porsolt, 2000; Borsini and Meli, 1988; Porsolt *et al.*,1978; Lucki,1997
Modified forced-swim test	High	High	Sensitive to acute antidepressant treatments; differentiates antidepressants from different classes including SSRIs	Lucki, 1997; Cryan and Lucki, 2000; Cryan *et al.*, 2002; Detke *et al.*, 1997; Molina and Tellez, 2001; Reneric *et al.*, 2001; Espejo and Minano, 1999; Stogner and Holmes, 2000
Tail suspension test	High	High	Sensitive to acute antidepressant treatments; certain strains climb their tail	Varty *et al.*, 2003; Chermat *et al.*, 1986; Thierry *et al.*,1986
Olfactory bulbectomy	Medium	High	Behavioral effects evident only following chronic treatment; mechanism of action poorly understood	Cairncross et al.,1978; Janscár and Leonard, 1984; McNamara *et al.*,1995; Redmont *et al.*,1997; Kelly *et al.*,1997; Mar *et al.*, 2000; Kelly *et al.*, 1997
Learned helplessness	Medium	Medium	Sensitive to short-term antidepressant treatments; ethical restrictions in some countries	Gambarana *et al.*, 2001; Vollmayr and Henn, 2001; Seligman *et al.*, 1975
Chronic unpredictable stress	Low	Low	Reliability has been questioned repeatedly; behavioral effects evident only following chronic treatment	Kessler, 1997; de Kloet *et al.*, 2005; Borsini, 1997; Willner, 1997
Muricide behavior	Low	Low	Central stimulants like d-amphetamine, some antihistamines, and some cholinergic drugs also inhibit muricide behavior.	Horovitz *et al.*, 1965; Willner, 1984
Separation model	Low	Medium	Best method with face and construct validity; TCAs selectively reduce the signs of despair.	Everett, 1966
Incentive disengagement	Low	Medium	Good predictive validity but not popular because of procedural problem.	Steru *et al.*, 1984
Operant reward	Low	Low	The newer antidepressants and MAO inhibitors are also active in this test.	O'Donnell and Seiden, 1983
Post swim grooming response	Medium	Low	Used to detect MAO B inhibitor activity.	Bhattacharya and Sen, 1991
Chemical-induced Reserpine (or tetrabenazine) syndrome	High	High	Used as a reliable initial method to detect antidepressant activity; mood lowering effect is unclear; Nonselective for all monoamines	Alpermann *et al.*, 1992; Pawlowski and Nowak, 1987; Porsolt *et al.*, 1991; Delina-Stula, 1980
Amphetamine potentiation	Medium	Low	Newer antidepressants are ineffective	Delina-Stula, 1980; Willner, 1984;
Apomorphine antagonism	High	High	Useful for rapid detection of antidepressant activity	Alpermann *et al.*, 1992; Porsolt *et al.*, 1991
Potentiation of tryptamine-induced convulsions	Medium	Low	Newer antidepressants are ineffective	Graham-Stula, 1971; Knoll, 1980; Ozaki *et al.*, 1960
Yohimbine potentiation	High	Medium	Rapid test for screening diverse group of antidepressants	Bourin *et al.*, 1988; Goldberg and Robertson, 1983
Potentiation of 5-HTP responses	Medium	Low	Predict anti-depressant drugs influencing 5-HT activity	Corne *et al.*, 1963; Martin *et al.*,1985
Potentiation of 1-DOPA induced response	Medium	Low	Potentiated by all classes of antidepressants except SSRIs	Willner, 1984
Genetic models	Low	High	Allows to study single gene; endophenotype interaction; no single vulnerability gene available; cannot model multigenic diseases; further validation needed	Urani *et al.*, 2005; Crawley, 2000; Ramboz *et al.*, 1998; Parks *et al.*, 1998; Heisler *et al.*, 1998; Cryan *et al.*, 2001; Miyakawa *et al.*, 2001

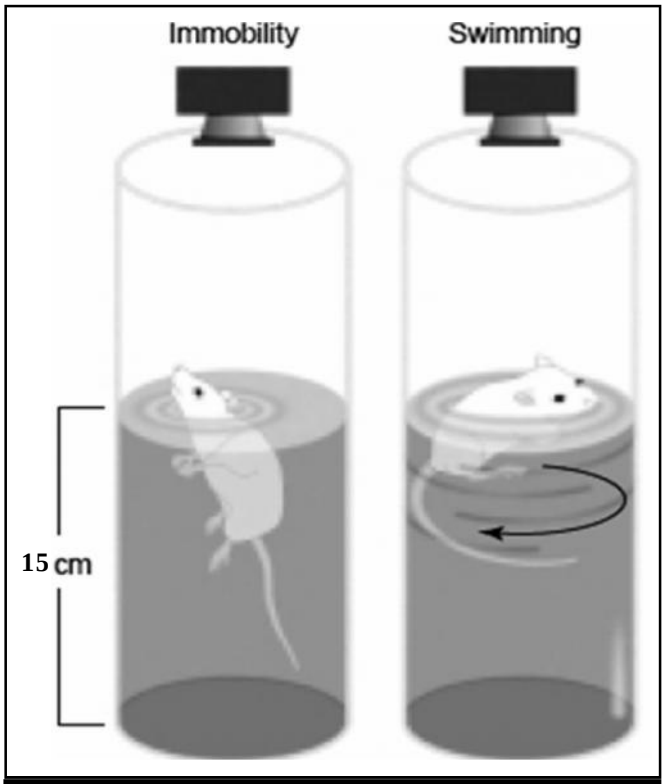

Fig. 1: Forced swim test

10 cm in diameter) and water level (15 cm) are different. The classical antidepressants reduce immobility time and a significant correlation exists between the experimental and clinical potencies of these drugs (Porsolt, 2000; Porsolt *et al.*, 1978).

However, the major drawback of the traditional FST is that it is unreliable in the detection of the effects of selective 5-HT reuptake inhibitors (SSRIs) and false positive results are induced by opiates and anti-histamines (Lucki, 1997).

Modified forced swim test :

In an effort to enhance the sensitivity of the traditional FST in the rat so that it can be SSRI responsive, several simple procedural modifications have been made (Lucki, 1997). These developments include increasing the water depth to 30 cm from traditional depths of 15–18 cm, and using a time sampling technique to rate the predominant behavior over a 5-s interval. These alterations enabled investigators to distinguish specific behavioral components of active behaviors, namely:

- climbing behavior (also known as thrashing), which is defined as upward-directed movements of the forepaws along the side of the swim chamber;

- swimming behavior, the movement (usually horizontal) throughout the swim chamber that also includes crossing into another quadrant; and

- immobility, which is defined, as in the traditional Porsolt test, as when no additional activity is observed other than that required to keep the rat's head above the water. As a result of the increase in water depth, there is considerably less immobility than in the traditional test because the animals cannot have contact with the cylinder bottom. The major advance of the modified FST over its traditional counterpart is that it reveals that catecholaminergic agents decrease immobility with a corresponding increase in climbing behavior, whereas 5-HT-related compounds such as SSRIs also decrease immobility but increase swimming behavior (Lucki, 1997; Cryan and Lucki, 2000). Recent studies have shown that 5-HT2C receptors play an instrumental role in mediating the effects of the SSRI fluoxetine in the test (Cryan and Lucki, 2000). Furthermore, it has been shown that the antidepressant-like behavioral effects of the noradrenaline reuptake inhibitor reboxetine in the FST are dependent on an intact ventral tegmental noradrenaline-mediated system but not the locus coeruleus system (Cryan *et al.*, 2002). One major drawback of the FST (as with many antidepressant-sensitive paradigms) is the fact that short-term antidepressant treatments reverse the immobility whereas in the clinic it can take weeks for the same antidepressants to elevate mood. However, it has been demonstrated that doses of antidepressant drugs that are inactive acutely elicit antidepressant-like effects when administered chronically, which further validates the modified paradigm (Detke *et al.*, 1997). Many other research groups have used this strategy with much success, indicating the reliability of the modified paradigm (Molina and Tellez, 2001; Reneric *et al.*, 2001; Espejo and Minano, 1999; Stogner and Holmes, 2000).

Tail suspension test :

The tail suspension test (TST) is not more than just a dry-land version of the FST. Like the FST, the TST is based on the observation that rodents (almost always mice) although gerbils and rats have been used after initial escape-oriented movements, develop an immobile posture when placed in an inescapable stressful situation (Varty *et al.*, 2003; Chermat *et al.*, 1986). In the case of TST (Fig. 2) the stressful situation involves the hemodynamic stress of being hung in an uncontrollable fashion by their tail whereas in the FST animals are placed in a cylinder filled with water (Thierry *et al.*, 1986). Unlike behavioral despair, there is no hypothermia and the behavioral changes last longer than the test period. Mice provide better results and in a typical experiment a mouse is hung (58 cm above a table top) on a wire in an upside down

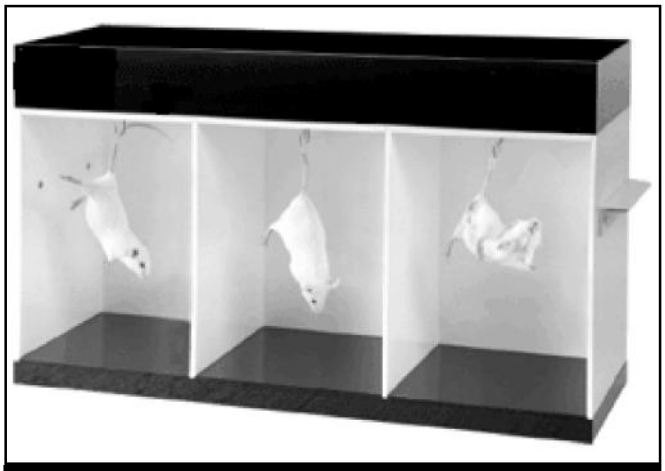

Fig. 2 : Tail suspension test

posture. After initial vigorous movements, the mouse assumes an immobile posture and the period of immobility during a 5 min observation period is noted. This test is a reliable and rapid screening method for antidepressants, including those involving the serotonergic system. However, MAO inhibitors are usually inactive (Chermat *et al*., 1986). The major drawback of this procedure is that it is sensitive only to acute antidepressant treatments and several mouse strains are essentially resistant to tail suspension induced immobility (Porsolt, 2000; Mayorga and Lucki, 2001).

Olfactory bulbectomy :

Bilateral olfactory bulbectomy in the rat is associated with changes in exploratory behavior that are reversed by chronic, but not acute treatment with antidepressant drugs (Cairncross *et al*., 1978; Cairncross *et al*., 1979; Leonard and Tuite, 1981; Janscár and Leonard, 1984). Many investigators have used this model to demonstrate the antidepressant activity of both, traditional as well as novel antidepressants (Briley *et al*., 1996; Hancock *et al*., 1995; McNamara *et al*., 1995; Redmont *et al*., 1997; Song and Leonard, 1994; Song *et al*., 1966a; Song *et al*., 1966b; Kelly and Leonard, 1994; Kelly and Leonard, 1995; Kelly *et al*., 1997; Redmont and Leonard, 1997). In this animal model of depression, animal is anaesthetized and olfactory bulbs are removed surgically. The animal is allowed to recover for 14 days after surgery and the behavior of the animal is assessed using open field apparatus (Cairncross *et al*., 1977). The antidepressant compounds preferentially enhance habituation to novelty in the bulbectomized rat and that these effects are not secondary to anosmia (loss of the sense of smell) (Mar *et al*., 2000). Concurrent with these studies, other groups have focused on neurochemical and physiological alterations that might account for the antidepressant-sensitive behavioral alterations. Much interest has been placed on the serotonergic system with a 5-HT hyperinnervation of the frontal cortex (Zhou *et al*., 1998) and stressor-induced alterations in 5-HT-mediated activity (Connor *et al*., 1999) observed subsequent to bulbectomy. Furthermore, increased striatal glutamate release during novelty exposure-induced hyperactivity has been demonstrated that might have a modulatory role on the antidepressant-sensitive response (Ho *et al*., 2000). Increases in the concentrations of the neuropeptides (or their encoding genes) corticotropin-releasing factor, thyrotrophin-releasing factor, somatostatin (Bissette, 2001) and neuropeptide Y (Holmes *et al*., 1998), which might play a role in mediating the antidepressant-sensitive behaviors, have also been demonstrated. Imaging studies demonstrated alterations in signal intensities in cortical, hippocampal, caudate and amygdaloid regions in olfactory bulbectomized animals, compared with sham-operated controls (Wrynn *et al*., 2000). In addition, ventricular enlargement was evident in bulbectomized animals. It has been suggested that these structural changes correlate somewhat with those seen in depressed patients (Wrynn *et al*., 2000). Comparing the behavioral and biochemical effects of bulbectomy in young versus aged rats, Slotkin and colleagues suggest that this test might provide a useful animal model with which to test therapeutic interventions for geriatric depression (Slotkin *et al*., 1999).

However, this model has one of the best portfolios for the prediction of known antidepressant compounds following repeated administration irrespective of their category but the procedure is quite time consuming and invasive with uncertainty in mechanism of action (Kelly *et al*., 1997; Cryan *et al*., 1998; Song and Leonard, 2005).

Learned helplessness :

This model is based on the assumption that, exposure to uncontrollable stress associated with repeated experiences of failure to escape from the stress, produces a 'helpless' situation, which results in performance deficits in subsequent learning tasks (Seligman *et al*., 1975; Martin *et al*., 1986). A typical experiment involves two parts:

Inescapable shock treatment:

Rats are subjected to foot shocks in a two compartment jumping box with the escape route to the adjoining unelectrified 'safe' chamber closed. A constant current shocker is used to deliver 60 scrambled shocks (15 sec duration, 0.8 mA every min) through the steel mesh grid floor. Control animals are placed in the chamber for 1 hr without experiencing shocks. This exercise is repeated 48 hr later on the day 3.

Conditioned avoidance training:

On the day 3, after the second inescapable shock treatment, the rats are subjected to avoidance training where a rat is placed in the electrified chamber and allowed to acclimatize for 5 min before being subjected to 30 avoidance trials, with an inter-trial interval of 30 sec. During the first 3 sec of each trial, a buzzer stimulus or a light signal (conditioned stimulus, CS) is presented, followed by foot shock (0.8 mA for 3 sec duration, unconditioned stimulus, UCS). The avoidance response is characterized by escape to the adjoining unelectrified chamber during CS, and is designated 'escape response'. Failure to exhibit escape response during CS is assessed as 'escape failure' which is said to represent depressive behavior (Martin *et al*., 1986). Antidepressants reduce or even eliminate escape failures. This model has excellent predictive validity and is extensively used to screen antidepressants, investigate their mode of action and to evaluate the neurobiology of depressive illness. Rats subjected to inescapable shock also exhibit decreased ambulation and aggression, and loss of appetite with weight loss, which can be utilized as additional investigative parameters (Seligman *et al*., 1975). The major drawback of the model is that most of the depression-like symptomatology does not persist beyond 2–3 days following cessation of the uncontrollable shock (Weiss and Kilts, 1998). A recent modification of the rat learned helplessness procedure incorporates aspects of the chronic mild stress paradigm (Gambarana *et al*., 2001). By chronic exposure to mild stressors the effects of the uncontrollable shock can be maintained for a prolonged period, and chronic treatment with the SSRI fluoxetine and the nonselective monoamine uptake inhibitor imipramine reversed these changes. The chronic stress procedure involves restraint and novel housing, and avoids the problems associated with food deprivation used in the traditional chronic mild stress procedure (Reid *et al*., 1997). Vollmayer and Henn have recently proposed key factors that can be manipulated to enhance both the usability and the reliability of the rat learned helplessness paradigm (Vollmayer and Henn, 2001). These include using a larger testing apparatus, a mild shock presentation and a relatively difficult shock avoidance task. Furthermore, they point out that animals can art factually avoid shock as a result of their position in the apparatus, which should also be taken into account (Porsolt, 2000).

Chronic unpredictable stress :

Exposure to stress or to traumatic life events has a strong impact on the manifestation of depression suggesting an impairment of proper stress coping strategies in depressed patients (Kessler, 1997; de Kloet *et al*., 2005). Consequently, the majority of animal models of depression are based on the exposure to various types of acute or chronic stressors. These paradigms are capable to consistently generate behavioral changes reminiscent of symptoms of depression, which can be reversed by antidepressant treatment. Chronic unpredictable stress is one of the most commonly used animal model for screening antidepressants. Several models have been used, mainly in rats, where, apart from chronicity of the stress, its unpredictability and inability to cope with the stressor are major factors (Stanford *et al*., 1996). In this technique, rats are exposed randomly to a variety of stressors during a 3 week period (Stanford *et al*., 1996; Katz, 1982). The stressors may include mild electric shock, immersion in cold water, tail pinch and reversal of light/dark cycle, overcrowding wet saw dust on the cage floor, tilting of the cage, flashes of light or loud sound, restraint, social isolation, food and/or water deprivation, foot or tail shock, attenuation of male sexual activity etc. The intervals between the different stressors are randomly programmed (unpredictability) between 10 and 100 sec. Control animals are placed in the test chamber but receive no stress. All these methods use the increase in plasma corticosterone as the stress indicator. The methods are sensitive to antidepressants of all classes including MAO inhibitors.

An alternative chronic stress model of depression (Willner, 1997), shown to have predictive validity and reliability, but not construct validity, involves exposure of rats or mice, sequentially over a period of weeks, to a variety of mild stressors, and the measure most commonly used to evaluate consequent depression is the decrease in consumption of a palatable sweet solution. The generalized decrease in responsiveness to rewards is comparable to anhedonia, the core symptom of the melancholic subtype of major depressive disorder. In a typical experiment, the rodent is exposed sequentially to a variety of mild stressors, including over-night illumination, periods of food and water deprivation, cage tilt, change of cage mate, periodic loud noise and change in the size of the home cage, which change every few hours over a period of weeks or months. The effectiveness of this procedure is usually monitored by tracking over repeated tests, a decrease in the consumption of and/or preference for a palatable weak (1-2%) sucrose solution. Typical and atypical antidepressants can restore normal behavior and perturbed physiological functions. The basic defect of this test, despite its utility in evaluating antidepressant activity, and the reason for its limited use, is the chronicity of the model and the difficulty to set it up in a new

laboratory. Considerable in-between laboratory variations also preclude wide acceptance of the model. Furthermore, the predictive, validity of this method does not appear to be superior to the widely used Porsolt's or the learned helplessness tests. Some investigations have questioned the reliability of this model since clinically effective antidepressants may fail to reverse the chronic stress induced physiological perturbations (Borsini, 1997).

Muricide behavior :

Muricidal, or compulsive mouse killing behavior, was noted in female rats of the Holtzman strain which instinctively attacked and killed mice irrespective of their satiety status (Horovitz *et al*., 1965). However, a small percentage of other rat species can also exhibit muricidal behavior (20% in Charles Foster and Wistar strains). Rats are prescreened for muricidal behavior, 48 hr before the test and the behavior is confirmed 24 hr later. The percentage of rats exhibiting muricidal behavior within 30 sec of introduction of a mouse into the rat cage is noted. Antidepressants attenuate muricidal behavior at doses below that inducing motor incoordination (as tested by the rota-rod method). The muricidal behavior is inhibited not only by antidepressants but also by central stimulants like d-amphetamine, some antihistamines, and some cholinergic drugs. Other psychotropic agents like neuroleptics, and benzodiazepines also block muricidal behavior at the doses that induce motor deficit. A major precaution is to remove the mouse carcass promptly to prevent it being eaten up by the killer rat. Rats exhibiting muricidal behavior can be reused but they have to be caged individually in isolation (Horovitz *et al*., 1965). Non-muricidal rats can be rendered muricidal by pretreatment with pilocarpine (2.5-5.0 mg/kg, ip) (Willner, 1984).

Separation models :

The rodent model was evolved on a primate model involving separation of the mother from its progeny. The initial stage of protest (agitation, insomnia, distress calls and screaming) is followed after 1 to 2 days by 'despair' (decreased normal activity, loss of appetite, reduced social interaction and vocalization). TCAs selectively reduce the signs of despair. The same protocol is followed in rats and the model is regarded as one of the best methods with face and constructs validity (Everett, 1966).

Incentive disengagement :

Rats are trained in a runway for food reward and then switched to non-reward situation (extinction of learning). Non-rewarded trials are followed by augmented locomotor activity in the first week and by reduced locomotor activity in the second week. Although the method has good predictive validity (Everett, 1966), it has not proved popular because of procedural problem.

Operant-reward test :

This model is based on the premise that hungry rats, trained to press a lever for food reward, find it difficult to desist from lever pressing if the reward is dependent upon the waiting. In a typical test, animals are trained to wait for 72 sec between lever presses to receive food reward. TCAs characteristically increase the number of food rewards that the rat earns under this schedule since lever pressing is closer to the original wait (72 sec) programme. The newer antidepressants and MAO inhibitors are also active in this test (O'Donnell and Seiden, 1983).

Post-swim grooming response :

This test, being a dopamine-mediated response, can be used to detect MAO B inhibitor activity. Groups of mice are placed in a water bath containing water (32^0C, depth 10 cm) for 3 min. Thereafter, the animals are removed and observed for grooming behavior, every min, during a 10 sec period, for 30 min. A score of one is given if the mouse was grooming during the 10 sec observation period or scored as 0 if not grooming. Thus each mouse could exhibit a maximum score of 30 (Bhattacharya and Sen, 1991).

Chemical-induced depression models :

Reserpine (or tetrabenazine) syndrome :

Reserpine depletes central and peripheral monoamines, whereas tetrabenazine has a selective central action. These drugs induce a syndrome (ptosis, hypothermia, catalepsy and decreased locomotor activity), the reversal of which is used as a reliable initial method to detect antidepressant activity. Reserpine (2.5-5.0 mg/kg, sc) or tetrabenazine (10mg/kg, ip) are used and the pharmacological effects are assessed 2 hr later. TCAs are effective in attenuating the syndrome both on pre and post treatment, whereas MAO inhibitors are effective only on pretreatment (Alpermann *et al*., 1992). In addition, the proconvulsant, blockade of conditioned avoidance response (Pawlowski and Nowak, 1987) in rodents, and emetic (pecking) response in pigeons, have also used as test parameters.

Reserpine-induced ptosis:

Ptosis or palpebral closure is graded from 0 to 4, 0 being complete closure and 4 indicating that the eyes are widely open (Pawlowski and Nowak, 1987).

Reserpine-induced decrease in locomotor activity:

Reduction in locomotor activity is best treated in an automated activity cage recording photobeam breaks as counts. Rats are placed individually and 10 min counts are recorded for 30 min, to obviate the initial locomotor spurt in ambulatory behavior (Alpermann *et al*., 1992).

Reserpine-induced hypothermia:

Rectal temperature, considered as the core body temperature, can be recorded using a multichannel telethermometer. The animal is placed in a loosely fitting perspex chamber and a thermistor probe is inserted 4 cm deep into the rectum (in rats), and kept *in situ* for the duration of the experiment. Temperature responses are noted before and 1, 2 and 4 hr after Reserpine administration. However, the reversal of hypothermia is not specific for antidepressants (Porsolt *et al*., 1991).

Reserpine-induced catalepsy:

A variety of methods can be used to assess catalepsy. The Pertwee's ring test has been shown to be sensitive in distinguishing between MAO A and MAO B inhibitors (Porsolt *et al*., 1991). The rat is placed on an iron ring (diameter 12 cm) fixed to a steel stand at a height of 15 cm. The time during which the rat remains motionless, with the complete cessation of snout and whisker movements, out of a total observation period of 5 min, is used to calculate percent immobility. A smaller ring (6 cm) can be used for mice.

The method is simple, rapid and reliable, and can detect all classes of antidepressants. Rats provide more cogent data than mice. However, false negatives (mianserin) and false positives (methyldopa, antihistaminics) are on record (Delina, 1980).

Amphetamine potentiation :

Most antidepressants, including TCAs and MAO inhibitors potentiate the central actions of amphetamine, including hyperthermia augmented locomotor activity, stereotypy and lethality in aggregated rodents (Delina, Stula, 1980).

Amphetamine-induced stereotypy:

Amphetamine (5-10 mg/kg, ip) induces a stereotyped behavior which is best noted 30 and 60 min after administration in rats (Willner, 1984; Alpermann *et al*., 1992). The rat is placed in a spacious cage in a dimly-lit quiet room. The latency of onset, intensity and duration of stereotypy, are assesses and scored-

- Discontinuous sniffing, constant exploratory activity

Continuous sniffing, periodic exploratory activity, small head movements

- Continuous sniffing, small body and head movements, discontinuous gnawing, biting and licking the cage wall, brief spurts of locomotor activity.
- Continuous gnawing, biting and licking of cage wall, no ambulation except for occasional backward movements.

Amphetamine-induced hyperthermia:

Temperature changes are recorded at 30 min intervals for 2-4 hr after administration of amphetamine (2.5-5.0 mg/kg, ip) by a telethermometer, as mentioned earlier, recording rectal temperature *Amphetamine-induced increase in locomotor activity*: Locomotor activity is recorded in an automated activity cage, as mentioned earlier, at 10 min intervals for 30 min, 2 hr after amphetamine (1-2 mg/kg, ip) (Willner, 1984).

***Amphetamine-induced toxicity in grouped rodents*:**

Mice are usually used and groups of 10 mice are kept crowded in a small wire mesh cage (16 cm^3). 30 min later amphetamine (10mg/kg, ip) is administered to the animals and lethality as compared to vehicle treated controls. This dose of amphetamine induces 20-30% mortality in mice. The relatively newer antidepressants, mianserin and trazadone are ineffective in this test (Alpermann *et al*., 1992).

Apomorphine antagonism :

Apomorphine in higher doses (16mg/kg, ip) induces hypothermia which is not antagonized by dopamine receptor blocking neuroleptics which can, however, attenuate apomorphine-induced stereotypy and climbing behavior. A wide range of antidepressants can, on the contrary, reverse the hypothermia. This method is simple and useful for rapid detection of antidepressant activity (Alpermann *et al*., 1992; Porsolt *et al*., 1991).

Potentiation of tryptamine-induced convulsions :

Tryptamine (60mg/kg, ip) produces bilateral clonic convulsive movements of fore paws in mice, characterized by pronounced up and down movements of the paws which push the animals backwards, resulting in retro-pulsion. TCA and MAO inhibitors potentiate a dose of tryptamine (15 mg/kg, ip) which produces minimal convulsions (Graham Smith, 1971; Knoll, 1980; Ozaki *et al*., 1960).

Yohimbine potentiation :

Yohimbine occupies central alpha receptors and

prevents norepinephrine from binding to these receptors. Compounds with antidepressant properties are known to inhibit physiologic inactivation of norepinephrine and other biogenic amines by blocking the uptake at nerve terminals. Yohimbine (25mg/kg, sc) produces minimal lethality in rodents. However, TCAs, MAO inhibitors and most of the newer antidepressants, potentiate the lethality of this dose of yohimbine in rats and mice. This test has been used as a simple and rapid test for screening diverse group of antidepressants (Alpermann *et al*., 1992; Bourin *et al*., 1988; Goldberg and Robertson, 1983).

Potentiation of 5-hydorxytryptophan (5-HTP) responses :

5-HTP, the 5-HT precursor, produces typical behavioral responses in rodents. The effect in rats, designated 'wet dog shakes', comprising of intermittent body movements including a shaking of the head, whereas, in mice, the effect is predominantly rapid and intermittent head-twitches. In mice, a dose of 5HTP (50 mg/kg, ip) which produces minimal head-twitch response is used, and the potentiation induced by drugs is noted by counting the twitches at three two minute intervals (19-21, 23-25 and 27-29 min) after 5-HTP administration. The final data is presented as the mean of the head-twitches during the test periods. This model can predict anti-depressants influencing 5-HT activity, namely selective 5-HT reuptake inhibitors like fluoxetine, and TCAs, like chlorimipramine (Alpermann *et al*., 1992; Corne *et al*., 1963; Martin *et al*., 1985) .

Potentiation of 1-DOPA induced response :

Mice are treated with 1-DOPA (25 mg/kg, i.p.) and benserazide hydrochloride (6.5 mg/kg, i.p.). The change in behavior is scored every 10 minute for 30 minutes (Alpermann *et al*., 1992). A scoring system, ranging from 1 to 4, is used, based on the following criteria:

- piloerection, minimal increase in ambulation,
- piloerection, marked ambulation, salivation, irritability,
- piloerection, profuse salivation, jumping, vocalization, increased ambulation,
- piloerection, profuse salivation, stereotypy (compulsive gnawing and biting the cage wall), reduced ambulation, aggressive behavior and automutilation (biting of tail and fore paws). The dose of 1-DOPA used produces minimal behavioral changes, which are potentiated by all classes of antidepressants except those acting selectively through increased 5-HT activity (Willner, 1984).

Genetic models :

There has been an upsurge in the development of mice with genetically altered expression of a specific protein, be it a receptor, transporter, enzyme or signal transduction protein. These new tools have the potential to examine novel targets for antidepressant activity for which there are few established pharmacological tools.

Genetically engineered mice have been successfully used to validate hypotheses illuminating the etiology of depression (Urani *et al*., 2005). The majority of studies use simple tests such as the forced swim test (FST) or tail suspension test (TST) to elucidate their behavioral changes. Some examples of knockout mice, such as those with targeted deletion of the 5-HT1A receptor and the noradrenaline transporter, are expected to show antidepressant-related phenotypes given the large body of evidence implicating these proteins in antidepressant action. In other examples, where selective pharmacological tools have been unable to penetrate, such as α2-adrenoceptor subtypes and signaling molecules such as the G protein G$z\alpha$, the behavioral evidence in mutant mice implicates these targets in antidepressant action and provides new directions for drug discovery. However, the much-discussed caveats associated with interpretation of the behavioral effects in genetically altered animals should not be understated (Crawley, 2000), the major two being background strain differences and compensatory adaptive changes. The ability to see the same phenotype across different strains, as in the case of 5-HT1A receptor knockout mice, gives further credence to the reliability of the phenotype (Ramboz *et al*., 1998; Parks *et al*., 1998; Heisler *et al*., 1998). The full potential of regionally selective and inducible knockout and transgenic mice has yet to be realized, but such strategies offer many advantages over currently used techniques. Such mice certainly will be welcome tools to dissect regionally specific circuits that might influence the actions of antidepressants. The ability to restore, albeit transiently, the phenotype in noradrenaline-deficient mice by administering the synthetic precursor L-deoxyphenylserine is a novel way to confirm that the phenotype is related to noradrenaline function as opposed to adaptive changes resulting from being reared without this monoamine (Cryan *et al*., 2001). Specific behavioral changes can be conformed by conducting multiple types of behavioral tests such as FST, TST and learned helplessness. Other physiological analyses such as tests for locomotor activity, pain sensitivity or cognition might be necessary to implicate behavioral changes to stress-induced depression. Such caveats cannot be underestimated and over interpretation of antidepressant-

like phenotypes must be avoided. For example, muscarinic acetylcholine M1 receptor knockout animals are hyperactive and correspondingly have an artefactual antidepressant-like phenotype in the FST. Brain-derived neurotrophic factor (BDNF) heterozygote knockout mice show altered behavior in the learned helplessness paradigm but this has been ascribed to their reduced sensitivity to pain as opposed to a depression related phenomenon (Miyakawa *et al*., 2001). Therefore, appropriate caution using other convergent tests that draw on different antidepressant-related endophenotypes and complementary physiological analyses provide a program of information concerning whether a given phenotype is functionally relevant to depression-related pathology.

Conclusion :

Animal models of depression have proven their great value in the identification and validation of monoamine-based antidepressant compounds. In particular, the FST and TST, but also most of the other models discussed in this review, show a relatively high predictive validity regarding antidepressant efficacy in patients. Despite the fact that none of the presently available animal model is able to replicate all aspects of depression and most likely never will, existing paradigms have proven extremely useful not only in the identification and improvement of antidepressant substances, but also in the validation of neurobiological concepts. All models presently available have been validated using compounds affecting the monoamine system. Therefore, a major yet unsolved question is whether these models will be adequate to detect compounds other than those related to monoamines, which is a prerequisite for establishing novel classes of antidepressants. The aspect of delayed onset of antidepressant action, as observed in human subjects, has been modeled by some of the paradigms. To strengthen paradigms modeling disease etiology to improve their reliability and to develop novel tests that will allow to pick up classes of antidepressants beyond monoamines pose major challenges for the future. Addressing endophenotypes related to human depression largely overcomes the inherent limitations of animals in the task of modeling the complex symptomatology of depression. However, the promising concepts attempting to model the etiology of human depression are still at the beginning and need to prove their value for understanding the neurobiology of this disorder.

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