INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Review Article

HOW TO TEST MEDICINES OF OBSESSIVE COMPULSIVE DISORDER??

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Article Received on: 17/10/12 Revised on: 01/11/12 Approved for publication: 19/12/12

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a psychiatric affliction with a lifetime prevalence of 1-3%. OCD is an anxiety disorder characterized by obsessive thinking (persistent ideas, thoughts, impulses or images that are experienced as intrusive and inappropriate) and compulsive behaviour (repetitive behaviours or mental acts [e.g. hand-washing, checking, praying, and counting]) that causes marked distress or significant impairment. During the last 30 years there have been many attempts to develop animal models of obsessive-compulsive disorder (OCD), in the hope that they may provide a path for furthering our understanding and treatment of this disorder. The present review article provides the reader with an overview of the currently active animal models of OCD with their strengths and limitations. We have reviewed the genetic, pharmacological, neurodevelopmental and behavioural animal models of OCD, and discussed their face validity (derived from phenomenological similarity between the behavior of the animal and the specific symptoms of the human condition), predictive validity (derived from similarity in response to treatment) and construct validity (derived from similarity in the underlying mechanisms).

Keywords: Obsessive-compulsive disorder, repetitive, compulsive, genetic model.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a psychiatric affliction with lifetime prevalence[1] of 1–3%. OCD is an anxiety disorder characterized by obsessive thinking (persistent ideas, thoughts, impulses or images that are experienced as intrusive and inappropriate) and compulsive behavior (repetitive behaviors or mental acts [e.g. hand-washing, checking, praying, counting]) that are time consuming (i.e. they take more than 1 h a day) or cause marked distress or significant impairment. Three major neurotransmitter systems have been implicated in the pathophysiology of OCD, the serotonergic, the dopaminergic and the glutamatergic[2]. The reports that serotonin reuptake inhibitors (selective and non-selective, i.e. clomipramine, SSRI's/SRI's) are effective in alleviating obsessions and compulsions in patients led to the hypothesis that dysregulation of the serotonergic (5-HT) system is involved in the pathophysiology of OCD[3]. Involvement of the dopaminergic system in the pathophysiology of OCD has been suggested on the basis of the benefits obtained with co-administration of SSRIs and dopamine blockers[4] as well as on clinical observations of obsessions and compulsions in basal ganglia-related disorders, such as Tourette's syndrome. It should be noted that it is difficult to distinguish between the involvement of the dopaminergic and serotonergic systems in OCD because there are complex interactions between these two neurotransmitter systems so that drugs that directly affect one system can also have an indirect effect on the other system. For example, 5-HT2c antagonists increase dopamine release. Involvement of the glutamatergic system has been recently suggested[5] on the basis of elevated glutamate levels in the cerebrospinal fluid of drug-naive patients[6]; correlations between symptom severity and the level of several glutamatergic metabolites; improvement of symptoms following treatment with riluzole, a glutamatergic antagonist, D-cycloserine (DCS), a partial N-methyl- D-aspartate (NMDA) agonist and memantine, a non-competitive NMDA antagonist[7]. In recent years there is a growing recognition that sex hormones play a modulatory role in OCD[8]. Life events related to the female hormonal cycle may trigger or exacerbate OCD in women patients[9]; and gonadotropin-releasing hormone (GnRH) agonists were reported to ameliorate OCD symptoms in OCD patients[10]. The understanding and treatment of OCD may benefit from appropriate animal models that closely mimic its behavioral and neural manifestations. In light of the accumulating evidence on sex differences in OCD it is highly important that animal models employ both male and female subjects.

Validation of animal models of OCD

Previous papers have provided a thorough discussion of criteria for the validation and evaluation of animal models of psychopathology in general and of obsessive-compulsive disorder (OCD) in particular. Ideally, an animal model of OCD would show the three types of validity. In the present paper we treat phenomenological similarity between the behavior in the animal model and the specific symptoms of the human condition as contributing to the face validity of a model; similarity in the mechanism (physiological or psychological) that induces behavioral symptoms and in the neural systems involved as contributing to construct validity; and similarity in response to treatment (pharmacological or other) as contributing to the predictive validity of the model and to its construct validity. In the field of animal models of OCD, a model's **face validity** is typically based on the induction of behaviors that are similar to compulsions in being repetitive, excessive and inappropriate. As the physiological and/or psychological causes of OCD are currently unknown, **construct validity** of animal modes of OCD can be established by demonstrating involvement of the serotonergic, dopaminergic and glutamatergic systems, the orbitofrontal cortex, cingulate cortex and basal ganglia, as well as by demonstrating modulation by ovarian hormones. In the field of animal models of OCD, **predictive validity** can be achieved by demonstrating similarity in response to pharmacological or neurosurgical treatment. The pharmacotherapy of OCD is unique in that to date only SSRI's/SRI's have been shown to be effective as a monotherapy. Therefore similarity in response to pharmacotherapy requires a demonstration of both sensitivity to SSRI's/SRI's and insensitivity to other classes of drugs, which are not effective in OCD (e.g. non-serotonergic antidepressants such as desipramine, anxiolytic agents such as diazepam, antipsychotics such as haloperidol).

Animal models of OCD

Animal models of OCD are typically divided into four classes according to the method used to induce obsessions and compulsive behavior.

A) Genetic models
B) Neurodevelopmental models
C) Pharmacological models
D) Behavioral models

Recently we have developed a novel animal model of OCD in which mice develop obsessions when subjected to continuous flickering light[10] (Patent No. 3087/DEL/2012) and perform repetitive actions (compulsive behavior) to neutralise the obsessions.

A) Genetic Models

There are eight mice models[11] of obsessive-compulsive disorder (OCD) in which compulsive-like behavior appears in mice following a known genetic manipulation, and one model in which compulsive-like behavior developed as a result of selective breeding. i) D1CT-7 transgenic mice, ii) Hoxb8 mutant mice, iii) 5-HT2c knockout mice, iv) Dopamine transporter knockdown mice, v) Aromatase knockout mice , vi) Sapap3 mutant mice, vii) Slitrk5 knockout mice, viii) Nest building behavior in house mice following selective breeding. The D1CT-7 transgenic mice, Hoxb8 mutant mice, 5-HT2c knockout mice and dopamine transporter knockdown mice were not created on the basis of a known mutation in humans that was found to be related to OCD. Rather, these models are based on behavioral similarity, that is, the behavior of genetically modified mice was found to be similar in specific respects to that of OCD patients. Dopamine transporter knockdown mice show behavioral abnormalities and response to treatment that may be relevant to attention deficit hyperactivity disorder, bipolar disorder and drug addiction. Aromatase knockout mice were originally developed to study the role of estradiol in the sexual differentiation of the reproductive system. Indeed, in a number of studies male knockout mice were found to exhibit abnormal reproductive behaviors. Aromatase knockout male mice exhibit a number of behavioral and neural abnormalities, which may be relevant to OCD as well as to other disorders. It is therefore unlikely that this model is a mouse model of OCD, although it may contribute to our understanding of the role of estradiol in compulsive behaviors. Compared to previous genetic models of OCD, the Sapap3 knockout model has two advantages. First, Sapap3 knockout mice show a more restricted profile of behavioral and neural abnormalities, all of which are relevant to OCD (in contrast to previous models, which showed abnormalities not typical of OCD, for example, obesity). Thus, Sapap3 knockout mice showed increased grooming and anxiety-like behaviors, and abnormalities in the striatum and the glutamatergic system. The second advantage of the Sapap3 model is that it is the first to support the relevance of the behavioral abnormalities to OCD by demonstrating that a SSRI produces a beneficial effect in the model. As was the case with Sapap3 mice, Slitrk5 knockout mice exhibit a restricted profile of behavioral and neural abnormalities, which are relevant to OCD. Thus, Slitrk5 knockout mice showed increased compulsive and anxiety-like behaviors, and the relevance of these behavioral abnormalities to OCD was supported by successfully demonstrating that a SSRI decreases these behaviors. Nest building behavior in house mice following selective breeding. Selective breeding of house mice (*Mus musculus*) over 55 generations resulted in a 40-fold difference between BIG and SMALL mice in the amount of cotton used for nest building. Because nest building behavior is a naturally occurring repetitive and stereotypic behavior, the excessive nest building in BIG mice may provide an animal model of OCD. BIG male mice may serve as a mouse model of OCD with good face validity, derived from increased nest building and marble burying, and good predictive validity, derived from their selective response to drugs that are effective in treating OCD patients. Of the genetic models, the BIG mice model has the most restricted behavioral profile, affecting only compulsive-like behaviors, and the best predictive validity, as this is the only model in which a drug that is not effective in OCD has been tested and shown not to be effective. Its predictive validity will be further supported by demonstrating that it is not responsive to additional classes of drugs, which are not effective in OCD.

B) Neurodevelopmental Models

The neonatal clomipramine model[12] is the first Neurodevelopmental model of obsessive-compulsive disorder (OCD). Neonatal rats are exposed to repeated injections of SRI (serotonin reuptake inhibitor) clomipramine (15 mg/kg, twice daily between postnatal days 9–16) and their behavior is assessed at adulthood. Regretfully, although there are plenty of data showing that male and female rats respond differently to neonatal manipulations, only the behavior of male rats was assessed. Clomipramine-treated adult male rats showed elevated anxiety, as measured in the plus-maze, less spontaneous alternation in a T-maze, and increased hoarding behavior, assessed by counting the number of accumulated food pellets at the bottom of the cage. In addition, these rats buried more marbles, which may reflect increased anxiety or increased compulsivity. Clomipramine-treated rats were found to show impairment in acquiring a win-shift task in an eight-arm radial maze and a visual discrimination task and its reversal in a T-maze. Interestingly, clomipramine-treated rats showed increased latency to choose arms and were reported to typically sit in front of an arm for a long time[12]. Andersen et al. (2010) also assessed the level of mRNA for 5-HT1a, 5-HT1d, 5-HT2c and D2 receptors in the striatum, orbitofrontal cortex and medial prefrontal cortex, and found only increased mRNA for 5-HT2c in the orbitofrontal cortex and for D2 in the striatum of clomipramine- treated rats compared with vehicle-treated rats. In addition, there was a strong correlation (r>0.76) between these two measures. The neonatal clomipramine model is promising in that some of the behaviors exhibited by the treated rats bear similarities to behaviors of OCD patients, and there is overlap between regions that may be involved in producing abnormal behaviors in the model and in OCD.

C) Pharmacological Models

Pharmacological models of obsessive-compulsive disorder (OCD) are based on chemical-induced behavioral alterations, which bear similarity to some clinical signs seen in patients diagnosed to be suffering from OCD.

i) Quinpirole – induced compulsive checking model

In this model, developed by Szechtman and colleagues (1998), rats are repeatedly injected with quinpirole, a D2/D3 agonist (twice a week at a dose of 0.5 mg/kg, over a 5-week period) and allowed to explore a large open field containing four small objects. After the 10th injection of quinpirole, the behavior of rats is observed for a duration of 55 min. Behavioral parameter such as: frequency of stops in each location (place or object); mean duration between two consecutive visits to a given location; mean duration of stopping in a given location; the number of visits to other

locations in between returns to a given location are observed in quinpirole and saline treated rats. Quinpirole-treated rats typically exhibit two favorite locations i.e. locations in which they stop up to 20 fold more compared to other locations. In addition, these rats return to these locations faster and they stop at fewer places during return visits[13]. The relevance of quinpirole-induced compulsive checking is based primarily on behavioral similarity, to repetitive actions performed by OCD patients. This analysis led Szechtman and colleagues to claim that quinpirole-induced compulsive checking meets formal ethological criteria of compulsive checking seen in OCD patients, including: (a) a preoccupation with and an exaggerated hesitancy to leave the items of interest, (b) a ritual-like motor activity pattern, and (c) dependence of checking behavior on environmental context. The quinpirole models shows excellent face validity, good predictive validity and construct validity in the neural systems. In addition, although dopaminergic involvement has been suggested in OCD, it is not clear what role dopamine plays in the pathogenesis of OCD, and therefore whether the fact that compulsive checking is induced by a dopaminergic manipulation contributes to the construct validity of this model.

ii) mCPP – induced persistence model

This model builds on the tendency of normal rats to show a side bias (directional persistence). In the initial stages of training in a non-match to sample task in a T-maze (termed rewarded alternation), and of the 5-HT agonist mCPP (meta-chlorophenylpiperazine) to lead to the re-emergence of this bias, even after extended training[14]. In this procedure, after 1 week of habituation to the T-maze, rats are trained in a non-match to sample task (receiving initially two, then four and finally eight trials per day) until all animals reach performance criterion. After this baseline stage (which lasts around 350 trials), administration of drugs begin. Rat's preference to one of the arms in the T-maze is estimated using a Persistence Index. After excluding the 25% of the rats which had the lowest Persistence Index scores, Tsaltas and colleagues (2005) found that 4 days of administration of mCPP resulted in enhancement of Persistence Index score. Pre-treatment for 20 days with fluoxetine, but not with desipramine or diazepam, prevented mCPP-induced increased persistence. Taken together, these results suggest that mCPP-induced increased persistence in a nonmatch to sample task may be a model of OCD with good predictive validity. The mCPP-induced persistence model is highly time consuming to run, as only the baseline phase requires hundreds of trials. Therefore, although this model has good predictive validity, it is not recommended as a screening test for anti-compulsive drugs.

iii) 8-OHDPAT – induced decrease in spontaneous alternation model

Spontaneous alternation refers to the natural tendency of rats to explore novel places sequentially and in succession[15]. 8-OHDPAT (8-Hydroxy-N,N-dipropyl-2-aminotetralin)-induced decrease in spontaneous alternation can be correlated to perseveration and indecision as clinical signs seen in OCD patient. The most common version of this model uses acute administration of the 5-HT1a agonist 8-OHDPAT to decrease spontaneous alternation. Specifically, food deprived rats are run in a Tmaze in which the two goal boxes (one black and the other white) are always baited with food reward. Each rat is given several trials a day[15], during which it is placed in the start box and allowed to choose one of the goal arms. The critical measure is the number of choices made until an alternation occurs (a score of 1 represents perfect alternation). Acute administration of 8-OHDPAT leads to a reduction in spontaneous alternation[15]. 8-OHDPAT-induced decreased alternation is prevented in males and females by repeated administration of the SSRI fluoxetine[15] and the SRI Clomipramine, but not by the tricyclic antidepressant desipramine. These findings lend the model predictive validity, and suggest that it may be a useful tool for screening anti-compulsive drugs. The finding that stimulation and lesion of the thalamic reticular nucleus decrease 8-OHDPAT-induced decreased alteration contributes, however, to the model's construct validity by demonstrating similarity in the neural systems involved. Further support for the construct validity of the 8-OHDPAT-

induced decreased alternation model comes from findings on the role of ovarian hormones. Specifically, there are sex differences in responsiveness to 8-OHDPAT (earlier for males), and symptom severity and response to treatment are modulated by ovarian hormones in females. These observations suggest that the 8-OHDPAT-induced decreased alternation model may serve to study the role of ovarian hormones in OCD. 8-OHDPAT-induced decreased alternation provides an animal model of OCD with good predictive validity with regard to pharmacotherapy but not with regard to HFS (High frequency stimulation). The finding that 8-OHDPAT-induced decreased alternation is modulated by ovarian and related hormones contributes to the construct validity of the model and suggests that it can be used to further study the role of these hormones in compulsive behaviors and to develop new lines of treatment on the basis of this knowledge. Therefore the 8-OHDPAT model, which is easy and cheap to run is recommended as a screening test for anti-compulsive drug activity in males and females, but not as a model system to study the neural mechanisms of OCD.

D) Behavioural Models

Recently we have developed a novel laboratory model viz flickering light induced obsessive-compulsive behavior model[16] (Patent No. 3087/DEL/2012).

Ethological models include naturally occurring repetitive or stereotypic behaviors, such as tail chasing, fur chewing and weaving; innate motor behaviors that occur during periods of conflict, frustration, or stress (displacement behaviors), such as grooming, cleaning, and pecking; and natural behaviors that occur following some behavioral manipulation, such as schedule-induced polydipsia[17] and food-restriction-induced hyperactivity. These models rest primarily on behavioral similarity between the behavior in the model and the clinical condition. The similarity may be evident at two levels: at the level of the specific behavior, e.g., grooming in animals and cleaning in patients; and at a more abstract level, e.g., the behavior induced in the model is repetitive as are compulsions.

i) Marble burying behavior model

Rodents use bedding material to bury noxious as well as harmless objects. Careful analysis of marble burying behavior led to the conclusion that this model does not resemble anxiety, but

may rather be related to compulsive behaviors[18]. Although earlier studies used mice, marble burying has recently also been tested in rats. In a typical experiment, the animal is placed in a clear cage bedded with 5 cm of sawdust, upon which glass marbles are arranged (9 for rats or 20 for mice). The animal is exposed to this cage containing marbles for 10 min (in case of rats) or 30 min (in case of mice). The number

of marbles buried during this period by the animals (covered two-thirds of the way or more) is recorded. A greater number of buried marbles represents a higher degree of compulsivity. When assessing the effects of drugs on marble burying it is critical to also assess drugs' effects on activity level, to refute the possibility that a reduction in marble burying reflects a non-specific decrease in behavioral output. In males, marble burying is decreased by SSRIs at doses that do not affect locomotion[19] and this suppressive effect is not exerted by desipramine. In another group (about 30%) of normally cycling female rats, marble burying was found to fluctuate along the estrous cycle, being higher during dietestrous compared with proestrous. There is also sufficient evidence that sex hormones modulate marble burying in males. Specifically, acute administration of the neurosteroid allopregnanolone or its precursor, progesterone as well as GnRH agonist leuprolide decreased marble burying but not locomotion. Serotonergic (5-HT1a and 5-HT7 receptors), dopaminergic (D2 receptors) and glutamatergic (NMDA receptors) have been shown to play a role in marble burying behavior of male rats and have been implicated in the pathophysiology of OCD. There is also evidence for the involvement of the nitric oxide system in marble burying behavior in male rats. Specifically, nitric oxide agonists and antagonists have been shown to increase and decrease marble burying, respectively, with no effect on locomotion. As there is some evidence for high nitric oxide levels in OCD patients, these findings contribute to the construct validity of the marble burying model. Marble burying model provides good face validity and some construct validity for testing anti-OCD agents. Its predictive validity should be regarded with caution. It is noteworthy that although marble burying cannot differentiate between anti-compulsive and anxiolytic drugs. It is the most straightforward and cost-effective procedure of all current animal models of OCD.

ii) Behavioral models of OCD based on perseveration

Recently perseveration occurring spontaneously in the 5-choice serial reaction time task[20] or following a change in task contingencies in reversal training[21] has been suggested to provide models of OCD, on the basis of studies reporting perseverative behavior during neurocognitive tasks in OCD patients. Perseveration in the 5-choice serial reaction time task (5-CSRTT). In this task, carried out with rats or mice, the animal is tested in an apparatus containing five food magazines. In each given trial a certain magazine is cued by a light stimulus in a random order and the animal learns to collect a food reward from the cued magazine. Perseveration in this task is defined as repeated responses to a specific magazine after it has been rewarded[20]. Perseverative responding in the 5-CSRTT has face validity and some construct validity. However, because perseveration is common in additional psychiatric and neurological disorders it is crucial to demonstrate that perseveration in 5-CSRTT is relevant to OCD by establishing its pharmacological predictive validity.

iii) Reversal training model

In a typical reversal learning task, once a rat learns to press one of two levers for a food reward, the reinforcement contingency is reversed, and the formerly non-reinforced lever becomes the reinforced lever and vice versa. Perseveration in this task is measured as the number of responses on the previously reinforced lever made before the animal reaches chance-level performance[21]. Reversal learning has also been assessed in primates, typically using visual discrimination rather than position discrimination. Once the animal learns to respond to one of two different visual stimuli presented on a screen in order to obtain a reward, the reinforcement contingency is reversed and the formerly non-reinforced stimulus becomes reinforced. Although perseverative responding during reversal training has face and construct validity, its pharmacological profile undermines the suggestion that this behavior may serve as a model of OCD.

iv) Schedule – induced polydipsia model

In this model[17], food deprived rats are trained to collect a food reward on a fixed-interval schedule (usually one to two food rewards every 60 s), while having free access to drinking water. Typically within 3–5 weeks of training in this reinforcement schedule rats begin to consume excessive amounts of water during training, that is, 5–10 times more than control rats that receive the same amount of food all at once. Polydipsic behavior has been suggested to be analogous to the repetitive and purposeless behaviors seen in OCD. In male rats, schedule-induced polydipsia (but not drinking in the control group) is reduced by chronic administration of the SSRIs/SRIs such as clomipramine, fluoxetine and fluvoxamine but is unaffected by chronic administration of the tricyclic antidepressant desipramine, the typical antipsychotic haloperidol or the anxiolytic diazepam[17]. These findings lend the model predictive validity, and suggest that it may be a useful tool for screening anti-compulsive drugs. Van Kuyck et al. (2008) found that high (100 Hz), but not low (2 Hz), frequency stimulation of the nucleus accumbens shell, the mediodorsal thalamic nucleus and the bed nucleus of the stria terminalis reduced polydipsic behavior in male rats. Support for the model's construct validity is provided by studies demonstrating the involvement of the serotonergic system in schedule-induced polydipsia. Acute administration of 5-HT2c agonists (Ro 60-0175/ORG 35030, Ro 60-0332/ORG 35035 and WAY 163909) decreased polydipsic behavior in both male and female rats without any effect on the amount of water consumed in control rats. Co-administration of fluoxetine and either the 5-HT1a antagonist WAY 100635 or the 5-HT1b partial agonist GR 127935 accelerated the ability of fluoxetine to reduce polydipsic behavior in male rats, whereas the administration of either WAY 100635 or GR 127935 alone had no effect. The various treatments did not affect water consumption in the home cage, suggesting that the effect was specific for polydipsic behavior. Schedule-induced polydipsia provides an animal model of OCD with excellent predictive validity and constructs validity. HFS (high frequency stimulation) had a selective inhibitory effect on polydipsic behavior, which contributes to the construct validity of the model, which is also strengthened by evidence for the involvement of the serotonergic system.

v) Spontaneous stereotypy in deer mice model

In this model, naturally occurring repetitive or stereotypic behavior of deer mice (*Peromyscus maniculatus bairdii*) is observed. Deer mice spontaneously develop stereotypic behavior consisting of vertical jumping, backward somersaulting and patterned running. Mice (male and female) are divided into high, low and non-stereotypic on the basis of a stereotypic score given to each rat following observation for several hours[22]. While stereotypic behaviors occur in additional neuropsychiatric disorders (e.g. autism, schizophrenia), the relevance of stereotypic behavior in deer mice to OCD is strengthened by the demonstration that they are decreased by repeated administration (for 21 days) of fluoxetine but not of desipramine[22]. The stereotypic

behaviors in both high and low stereotypic mice were decreased by repeated (4 days) systemic administration of the 5-HT2a/2c agonist mCPP and of the D2/D3 agonist quinpirole[22]. The construct validity of this model is supported by an additional line of studies. High stereotypic mice showed decreased enkephalin content and increased dynorphin/ enkephalin ratio in the striatum, compared with low stereotypic mice. These results suggest that high stereotypy may be mediated by increased activity in the direct basal ganglia thalamo-cortical pathway and decreased activity in the indirect pathway. Moreover, imbalance between the direct and indirect pathways has been suggested to underlie compulsions in OCD, and D1 antagonists have been suggested to ameliorate compulsions. In addition, because in this model stereotypy develops spontaneously, it may provide insight into a range of genetic and environmental etiologic factors of OCD. An advantage of this model is that both male and female mice can be tested.

vi) The signal attenuation model

The signal attenuation model has been developed by Joel and colleagues[23] on the basis of the theoretical proposition that compulsive behaviors result from a deficit in the feedback associated with the performance of normal goal-directed responses. In this model, the normal behavior is lever-pressing for food, and the feedback for the response is an external stimulus, which follows the lever-press response and is accompanied by the presentation of the food reward. Thus, the stimulus signals that the lever-press response was effective in producing food. The deficiency in response feedback is simulated by extinguishing the contingency between the stimulus and the reward ("signal attenuation"). The procedure used to establish a stimulus as a response feedback and to test the effects of signal attenuation on the performance of this response has been termed post-training signal attenuation. The post-training signal attenuation procedure includes four stages. First, a stimulus (typically the magazine light and a tone) is established as a signal for the delivery of food by repeatedly pairing it with food (magazine training). Next, rats are trained to lever-press for food, whose delivery is accompanied by the presentation of the stimulus (lever-press training). Because rats experience the stimulus before they find the food, the stimulus comes to signal that the lever-press response was effective in producing food. In the third stage (signal attenuation), the stimulus is repeatedly presented without food (the levers are not present at this stage). It is hypothesized that the extinction of the stimulus–food contingency in this stage attenuates the "signaling" property of the stimulus. In the last stage (test), the effects of signal attenuation on rats' lever-press behavior are assessed under extinction conditions, i.e. pressing the lever results in the presentation of the stimulus but no food is delivered. Finally, the effects of signal attenuation on lever-press responding are assessed under extinction conditions (i.e. pressing the lever results in the presentation of the stimulus but, no food is delivered). As a consequence of signal attenuation (resulting in failure to get positive feedback), animals attempt repetitive lever pressing (compulsive behavior) so as to obtain reward (food), which is both excessive and unreasonable, as are compulsions seen in OCD patients. An anti-compulsive effect in the model is evidenced in a decrease in the number of "compulsive" lever -presses. In male rats, acute administration of the SSRIs paroxetine and fluvoxamine exerted an anti-compulsive effect, whereas acute administration of the tricyclic antidepressant desipramine, the anxiolytic diazepam and the antipsychotic haloperidol, did not exert this effect, supporting the predictive validity of the model. The signal attenuation model also has good predictive validity with regard to HFS (high frequency stimulation) as HFS of the subthalamic nucleus was found to exert an anti-compulsive effect. The findings with HFS also contribute to the construct validity of the signal attenuation model by demonstrating similarity in the neural systems involved. There is also evidence for the involvement of ovarian hormones in compulsive lever pressing. Thus, compulsive lever-pressing in females was found to fluctuate along the estrous cycle; acute administration of estradiol to prepubertal female rats attenuated compulsive lever-pressing; and withdrawal from chronic administration of estradiol increased compulsive lever-pressing in pre-pubertal female rats. The signal attenuation model has strengths and weaknesses as an animal model of OCD. The signal attenuation model has good predictive validity, as it can differentiate between the effects of SSRI's and of drugs not effective in the treatment of OCD. It requires, however, special equipment (operant boxes) and about 2 weeks of behavioral training. In addition, the post-training signal attenuation procedure is not well suited for chronic drug administration studies because repeated drug administration may affect behavior in the early stages of the procedure. The finding that compulsive behavior observed in this model (excessive lever pressing) has similarities to compulsive behaviors in patients in terms of response to treatment and neural systems involved suggest that this model may be useful in the study of the neurobiological mechanisms of compulsive behaviors. This is a cost effective model which is widely validated and used for screening of anti-OCD agents.

vii) Flickering Light induced Obsessive Compulsive behavior Model

The newly developed device[16] (Patent No. 3087/DEL/2012) comprises of a peculiar chamber, which has mirrors on its all four walls, thermocol pieces wrapped with glazed paper at the floor of the chamber and four flickering bulbs (15 watt each) at the ceiling of the chamber. The size, shape and material of the device could vary depending on the size of the animal to be accommodated conveniently. In the present invention, we used a rectangular plywood box of dimensions 36×30×45 cm^3 with mice as laboratory animals. The size of the box would increase suitably, if rats are to be used as laboratory animals. The thermocol pieces (4×3×1 cm^3) wrapped with glazed paper were provided at the floor of the chamber for quantifying the gnawing behavior. The mirrors attached to the four walls of chamber helped in producing a unique novel environment & enhanced the flickering effect of the bulbs by forming multiple images. When a mouse was kept in this peculiar chamber and was exposed to continuous flickering light for a period of 60 min., it showed a unique behavior marked by gnawing of the pieces of thermocol. This repeated gnawing behavior of the animal was correlated with the repetitive rituals or compulsive actions shown by the patient suffering from Obsessive Compulsive Disorder. Furthermore, this repetitive gnawing behavior of mice was successfully reversed by different categories of established anti-OCD medicines. At present following categories of medicines are prescribed by psychiatrists for the treatment of OCD- (a) Venlafaxine (serotonin-norepinephrine reuptake inhibitor), (b) Fluoxetine (Selective serotonin reuptake inhibitor), (c) Lorazepam (Benzodiazepine agonist) & (d) Haloperidol (Dopamine antagonist). Therefore, we studied the efficacy & utility of the newly developed model using

above medicines. The findings of the present study were highly promising & indicated that these medicines could be detected for their anti-compulsive effect employing the newly developed laboratory model. Furthermore, these mice behaved like normal mice after seven days of the experiment. Therefore, this device would find immense application in screening new anti-OCD medicines.

Advantages of the newly developed OCD model

- This is a very simple & cost effective model.
- Mild aversive environment viz. flickering of light evokes compulsive behavior (gnawing behavior) in mice similar to Obsessive-compulsive behavior of human beings.
- No special skill is required in handling this device.
- The repetitive gnawing behavior observed in this model is not habit forming.
- Currently, marketed medicines for OCD such as venlafaxine, fluoxetine, haloperidol & lorazepam etc. could be detected using this new model. Therefore, new medicines possessing anti-OCD potential can be screened using this device.
- There are no adverse stimuli or torture such as electric shock to the animals in this model.
- This model provides an animal model of OCD with good face validity, excellent predictive validity with regard to pharmacotherapy and HFS and fine construct validity.

CONCLUSION

Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by absurd, recurrent and persistent thoughts (obsessions) followed by certain stereotyped actions (compulsions). The common types of Obsessions are related to contamination, pathological doubts, somatic dysfunctions, need for symmetry, aggression etc. The classical forms of compulsions include checking, washing, counting etc. For obvious reasons, the understanding and treatment of diseases such as OCD must rely heavily on appropriate animal models that closely mimic their behavioral and, if possible, their neural manifestations. During the last 3 decades, several animal models of OCD have been developed. These models can be divided into four classes: genetic, neurodevelopmental, pharmacological and behavioral models. We have discussed the applications, utility and face validity (derived from phenomenological similarity between the behavior of the animal and the specific symptoms of the human condition), predictive validity (derived from similarity in response to treatment) and construct validity (derived from similarity in the underlying mechanisms) of these models in the present article.

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Source of support: Nil, Conflict of interest: None Declared

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