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EXPLORING GENETIC, PHARMACOLOGICAL, BEHAVIORAL AND NEURODEVELOPMENTAL ANIMAL MODELS FOR OBSESSIVE COMPULSIVE DISORDER

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ABSTRACT

Background: Obsessive compulsive disorder (OCD) is a disabling and common neuropsychiatric condition of poorly known etiology. Many attempts have been made in the last few years to develop animal models of OCD with the aim of clarifying the genetic, neurochemical, and neuroanatomical basis of the disorder, as well as of developing novel pharmacological and neurosurgical treatments that may help to improve the prognosis of the illness. The latter goal is particularly important given that around 40% of patients with OCD do not respond to currently available therapies. OCD is a mental disorder in which alteration of brain neurotransmitters take place and these alterations applicable for producing. Comprehensive search reveals that people with schizophrenia seem like they have lost contact with reality and remitting disorder associated with significant impairments in social, vocational functioning and shortened lifespan.

Objective: Many efforts have been made in the last few years to develop animal models of OCD with the objective of clarifying the genetic, neurochemical, and neuroanatomical basis of the disorder

Methods: These types of animal behavior models are introduced for evaluation of OCD symptoms and furthermore it's a good approach before going on clinical studies in human participants. Throughout the review article various animal models used for the determining the OCD symptoms.

Result: OCD can be complicated and hard to understand. It can be difficult to recognize in both children and adults. However, there is always hope for a better life free from OCD. A number of animal behavioral models such as genetic model, pharmacological model, behavioral model, neurodevelopmental model in mice were compiled in this review for easy learning or assessing behavioral parameters of OCD.

Conclusion: In the previous clinical or preclinical studies symptoms like Marble-burying, anxiety, and repetitive gnawing behavior are seen in OCD affected people. Moreover, symptoms are assessed by conducting behavioral, biochemical and neurochemical estimation on rodent/human trial. Animal models have been based on the management of behavioral parameters believed to be involved in OCD. This review provides a brief overview of behavioral animals models used for the diagnosis of OCD.

***Keywords*:** *obsessive compulsive disorder, genetic model, pharmacological model, behavioral model and neurodevelopmental model.*

INTRODUCTION

Obsessive compulsive disorder (OCD) is a disabling psychiatric condition characterized by the presence of upsetting, persistent thoughts, images, or impulses that are experienced as intrusive and senseless, and which cause marked distress or anxiety (obsessions) and/or excessive repetitive intentional behaviors or mental acts (compulsions) intended to neutralize this distress [1]. The disorder has a lifetime prevalence of 2.3% and it significantly interferes with social adjustment, employment, marriage, family relationships, and socioeconomic status [2-4]. OCD is a clinically heterogeneous and etiologically complex condition characterized by the presence of upsetting, persistent thoughts, images, or impulses that are experienced as intrusive and senseless, and which cause marked distress or anxiety (obsessions) and/or excessive repetitive intentional behaviors or mental acts (compulsions) intended to neutralize this distress [5]. OCD was found to be the fourth most common mental illness after drug abuse and major depression [6].

Depending on the method used to induce compulsive-like behavior, animal models of OCD are traditionally divided into four classes: genetic, pharmacological,

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behavioral manipulation, and neurodevelopment.

GENETIC MODELS OF OCD

1. DICT-7 transgenic mice

DICT-7 mice, developed by Burton *et al.,* are transgenic mice expressing a neuropotentiating protein (cholera toxin A_1 subunit) within a cortical-limbic subset of dopamine D_1-receptor expressing (D_1+) neurons. These mice were observed to exhibit abnormal behaviors, including episodes of perseverance or repetition of normal behaviors such as digging, grooming, and climbing, repetitive leaping, and non-aggressive repeated biting of siblings during grooming [7-8].

2. Hoxb8 mutant mice

Hoxb8lox mutant mice, developed by Greer and Capecchi in 2002, have been reported to exhibit OCD-like increased persistence of self-directed grooming and body licking, as well as mutual grooming of other mice [9-10].

3. 5-HT_{2c} receptor knockout mouse

5-HT_{2c} receptor KO mice were described by Chou-Green *et al.,* to display compulsive-like behavior, comprising more chewing of nonnutritive clay, a distinct pattern of neat chewing of plastic-mesh screen, and reduced habituation of head-dipping activity [11-12]. These mice also showed enhanced reversal learning with a decrease in trials, correct responses, and omissions to criterion, supporting the involvement of 5-HT_{2c} receptors in the cognitive mechanism underlying spatial reversal learning [12-13]

4. Aromatase knockout mice

Aromatase knockout mice were originally developed to study the role of estradiol in the sexual differentiation of the reproductive system [14-15]. They lack a functioning aromatase enzyme and are therefore estrogen-deficient. Male, but not female, knockout mice exhibited increased wheel-running activity and grooming but decreased ambulatory activity [16-17]. They also showed a decrease in catechol-*O*-methyltransferase activity in the hypothalamus. However, in addition to these compulsive-like behaviors, these mice also show other behavioral abnormalities that have been linked with other disorders such as schizophrenia, for example, a decrease in pre-pulse inhibition and an increase in amphetamine-induced activity [18-19].

PHARMACOLOGICALLY INDUCED ANIMAL MODELS OF OCD

Pharmacological models are based on drug-induced behavioral alterations that are similar to specific OCD symptoms in humans, such as perseveration, indecision, or compulsive checking, as well as increased anxiety. Construct validity of these models is based on the fact that these abnormal behaviors are induced by manipulation of neurotransmitter systems that are thought to be related with OCD, mainly the serotonin and dopamine pathways. Two of the most widely studied animal models of OCD, the 8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide (8-OHDPAT) induced decreased alternation and quinpirole-induced compulsive checking models, belong to this group.

1. 8-OHDPAT-induced decrease in spontaneous alternation

Yadin *et al.,* were the first to suggest that a pharmacologically induced decrease in the natural tendency of rats to explore novel places sequentially and in succession, what is known as spontaneous alternation, might serve to model two specific aspects of OCD, namely perseveration and indecision [20-21]. The most common version of this model uses acute administration of the 5-HT_{1a} agonist 8-OHDPAT to decrease spontaneous alternation both in rats and mice [22-25].

2. Quinpirole-induced compulsive checking

This model, developed by Szechtman *et al*., refers to the behavioral changes observed in rats after chronic treatment with the D_2/D_3 dopamine agonist quinpirole (0.5 mg/kg twice weekly for 5 weeks) [26-28]. When placed in a large open field with four small objects present at fixed locations, and over a period of 55 minutes in which they were videotaped, quinpirole-treated rats gradually developed a preference for two locations, at which they stopped more frequently (up to 20 times more) than did saline-treated rats. They exhibited much shorter return times to these places and stopped at fewer places between returns, as compared with control rats [26, 29].

3. Quinpirole-induced water contrafreeloading (CFL)

Besides compulsive checking, repeated administration of quinpirole also produces an increase in CFL, a phenomenon that occurs when animals, offered a choice between working for food (for instance, by

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lever-pressing) and obtaining it for free, consume a high proportion of their food from the source which requires effort [30-33]. Alongside this increase in the fraction of water obtained by operant responding (percentage of CFL), quinpirole-treated mice show a reduction in the total amount of water intake, that is, hypodipsia. Administration of the serotonergic agent clomipramine prevents the development of both CFL and hypodipsia induced by quinpirole, while haloperidol, a classical antipsychotic with D_2 antagonist activity, prevents CFL but not hypodipsia [34].

4. Meta-chlorophenylpiperazine (mCPP)-induced directional persistence in reinforced spatial alternation

Administration of mCPP, a nonspecific serotonin agonist, which mainly acts at the 5-HT_{2c}, 5-HT_{1d}, and 5-HT_{1a} receptors, increased directional persistence in a reinforced delayed alternation task. This mCPP-induced persistence was reduced by chronic administration of fluoxetine for 20 days but not by desipramine or a benzodiazepine. Challenge with a 5-HT_{2c} antagonist, but not a 5-HT_{2a} antagonist or a 5-HT_{1b} agonist, reduced mCPP-induced persistence, thus underlining the importance of 5-HT_{2c} receptors in this compulsive-like behavior [33, 35-36].

BEHAVIORAL MANIPULATION-BASED ANIMAL MODELS OF OCD

1. Marble burrying behaviors

In response to an aversive stimulus, many rodents (including rats and mice) exhibit burying behavior, commonly referred to as "defensive burying" [37-39]. Earlier several studies consider marble burying as a potential anxiety model [40-41], but now it has also been used as animal model to evaluate OCD [42-44]. Digging and burrowing are typical behaviors of mice species [45]. Marble burying is related to digging behavior and may in fact be considered as a more appropriate of repetitive digging. Mice show digging behavior in the response of novel environment. Marble-burying is a natural defense mechanism which appears in the state of stress. Marble-burying helps in measuring the amount of digging. In this model, mice were individually placed in separate plastic cages (21×38 ×14cm) containing 5 cm thick sawdust bedding. 20 clean glass marbles (diameter ~10mm) were arranged evenly on the bedding. After 30 minutes exposure to the marbles, mice were removed, and unburied marbles were counted [46]. A marble was considered buried, if its two-third size was covered with sawdust. The total numbers of marbles buried were considering as index of OCD. Valproate, carbamazepine and lamotrigine reduce marble-burying behavior suggesting that GABAergic mechanism is involved in marble-burying behavior and. Moreover, valproate reduces marble-burying behavior is a GABA (A) receptor-dependent [47, figure 1].

Fig. 1: Animal model for assessment marble burying behavior

2. Open field apparatus

The Open Field Maze is one of the most widely used platforms in animal behavioral studies [48]. The open field is also a very popular animal model of anxiety-like behavior and commonly used as a mechanism to assess the sedative, toxic, or stimulant effects of compounds [49]. Each animal was individually placed in a Plexiglass box (72×72× 36cm) and allowed to freely explore for 5 min. Behavior including time and frequency in center (18×18 cm) were recorded. [50-52]. Principally, the open field is an enclosure, generally square, rectangular, or circular in shape with surrounding walls that prevent escape. The most basic and common outcome of interest is "movement"; however, this can be influenced by motor output, exploratory drive, freezing or other fear-related behavior, sickness, relative time in circadian cycle, among many other variables. Distance moved, time spent moving, rearing, and change in activity over time are among many measures that can be tabulated and reported. Some outcomes, particularly defecation, center time, and activity within the first 5 minutes [52-55]. For each rat the Locomotion behaviors were recorded [56, figure 2].

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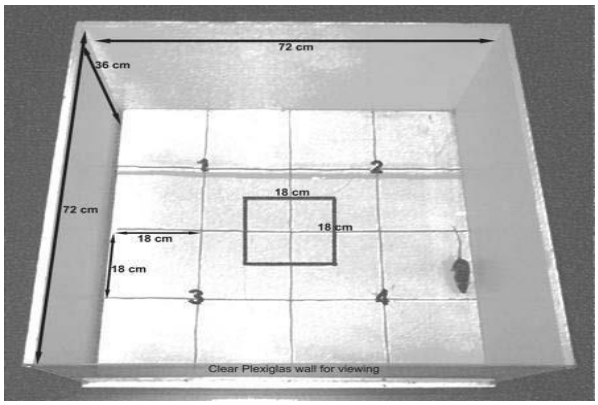

Fig. 2: Open Field Apparatus

3. Signal attenuation model

The signal attenuation model was developed by Joel in 2006 to examine the role of the striatum in compulsive behavior, especially in rats with lesions in the orbitofrontal cortex (OFC) [57]. Lesions in the rat OFC leads to a higher amount of compulsive lever-pressing. It was found that primary pathology of the OFC cause dysregulation (decrease) of Dopamine, Glutamate, GABA and serotonin in the striatum [58-59]. Compulsive behavior is induced by attenuating a signal indicating that a lever-press response was effective in producing food. In this model, the goal-directed behavior is lever-pressing for food, and the feedback cue is a stimulus that accompanies the delivery of food. To attenuate the signaling property of the stimulus, the latter is repeatedly presented without food, and the effects of this signal attenuation are finally assessed under extinction conditions (pressing the lever results in the presentation of the stimulus, but no food is delivered). To control for the effects of extinction per se, the behavior of these rats is compared with that of others in an extinction session that was not preceded by a signal attenuation process (regular extinction). Compulsive behavior is induced by attenuating a signal indicating that a lever-press response was effective in producing food. Pathology of the OFC leads to a dysregulation of the serotonergic system which is manifested in compulsive behavior. Serotonergic system is involved in orbital lesion-induced compulsivity [58, 60].

4. Flickering light induced obsessive-compulsive behavior model

It was observed that when mice were exposed to flickering light continuously for a period of 1hour they produced repetitive gnawing behavior [61-63]. This behavior was correlated with compulsive action of patients suffering from OCD. It is possible that mice experienced abnormal situation, when they were exposed to mild aversive environment such as flickering light in the present model leading to continuous biting of objects present in their surroundings. Rats were provided small pieces of thermocol, which were wrapped with glazed paper as novel objects. A mouse was kept in the unique chamber consisting of mirror on its four walls & flickering bulbs (15 watt) at the ceiling of the chamber. The dimensions of this unique plywood box were 36cm×30cm×45cm [62, 64]. The thermocol pieces (4cm3×3cm3×1cm3) wrapped with glazed paper were placed at the floor of the chamber uniformly. Then this mouse was exposed to flickering light for a period of 60 min. produced by four bulbs (15 watt) each fixed at the ceiling of the chamber to which animals had no access. All the thermocol pieces were removed from the unique chamber at the end of the experiment & total number of gnawed pieces of thermocol were counted [figure 3]. It was observed that there was a significant increase in the number of gnawed pieces of thermocol, when mouse was exposed to flickering light in the unique chamber from where there was no escape. This repetitive gnawing behavior of mice was successfully reversed by established anti-OCD medicines such as fluoxetine, venlafaxine, haloperidol & lorazepam. Furthermore, these animals behaved like normal mice after four days of the experiment [64].

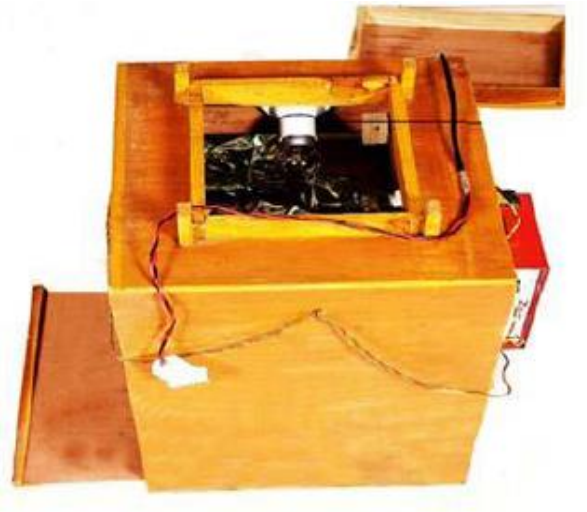

Fig. 3: Flickering light induced obsessive compulsive behavior model

5. Spontaneous stereotypy in deer mice

This model is based on the fact that deer mice (*Peromyscus maniculatus bairdii*) show spontaneous

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stereotypic behaviors consisting of vertical jumping, backward somersaulting, and patterned running [65-67]. Depending on the frequency of these behaviors, deer mice can be classified into high-, low-, and non-stereotypic mice. Both high- and low-stereotypic deer mice have been used as models of OCD, in some studies comparing them with non-stereotypic ones. Although both male and female mice were used in the studies, the potential influence of sex on the results was not analyzed [68].

NEURODEVELOPMENTAL ANIMAL MODELS OF OCD

1. Neonatal clomipramine

In 2010, Andersen *et al*., claimed to have developed a multiple OCD-like behavior model in rats [69-70]. They compared rats treated with 16 intraperitoneal injections of 15 mg/kg of clomipramine administered across postnatal days 9-16 with those receiving a saline vehicle following the same pattern of administration. Clomipramine-exposed rats showed more anxiety-like behavior in the elevated plus maze and a directed anxiety response in the marble-burying task, burying more foreign/novel objects. They also showed more perseveration in a reversal task, a general impairment of discrimination learning, and increased hoarding behavior. Besides these behavioral changes, regional biochemical differences were also observed in rats exposed to clomipramine, namely increased RNA messenger expression for 5-HT_{2c} receptors in the OFC and D_2 receptors in the striatum. None of these behavioral or biochemical changes were detected if clomipramine was administered in adult rats at postnatal days 50-57 [71-72].

CONCLUSION

This current article have to highlights a number of possible animals behaviorial models such as Marble burying behaviors, Open field apparatus, Signal attenuation model, Flickering light model in mice**,** which have been observed in individuals with OCD. OCD is an extremely debilitating condition that causes the patient distress and a reduction in quality of life. A link between childhood trauma and obsessive-compulsive symptoms has been reported in some studies. More research is needed to understand this relationship better many animal models have been generated in the last decades to explore different aspects associated with OCD from a range of perspectives, including pharmacological manipulation, genetic selection, and the analysis of behavioral patterns or neurocognitive function. OCD is a severe psychological sickness in which people interpret actuality abnormally. Comprehensive treatment entails a multi-modal approach, including psychopharmacology, psychosocial interventions, assistance with housing and financial sustenance etc., are utilize in the treatment of OCD and are proved to be effective in the management of OCD symptoms. Combining several animal models of OCD in order to detect anti-compulsive activity of new drugs might therefore constitute an interesting therapeutic option. The area of research where convergence is greatest involves the role of ovarian and related hormones in compulsive behavior. Imaging studies have shown differences in the frontal cortex and subcortical structures of the brain in patients with OCD. There appears to be a connection between the OCD symptoms and abnormalities in certain areas of the brain, but that connection is not clear. Future research with enhanced transgenic and imaging technologies will continue to improve our understanding of the relationship between aromatase and neurobehavioral functions. Animal models support us to elucidate complex mechanisms and provide a reasonably reliable platform to test the prospective of new substances. Emphasis is placed on the critical evaluation of currently available models because these models help to shape the direction of future research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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