International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS | Volume 8 | Issue 2 | APR-JUN | 2018 | 468-474
Review Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

A SYSTEMATIC REVIEW ON ANIMAL MODELS OF SUICIDE AND TRAIT RELATED BEHAVIOUR

Reshma Nehere[1] and Padmaja Kore[2]

[1,2*]**Department of Pharmacology, Modern College of Pharmacy, Yamunanagar, Nigdi, Pune, India.**

***Corresponding Author Email: padmaja.kalshetti@gmail.com**

ABSTRACT

Suicide is a leading cause of death worldwide. Though a sizable proportion of deaths by suicide may be preventable, it is well documented that despite of major governmental and international investments in research, education and clinical practice suicide rates have not diminished and are even increasing among several at-risk populations. Animal models are critical resources to help in understanding of delineate treatment targets and pharmacological means in improving our ability managing the risk of suicide. Certain behavioural traits related to suicidal behaviour as aggression, irritability, impulsivity and active avoidance can be modeled in laboratory animals. We broadly described various behavioural traits found clinically and their correlation in various pre-clinical animal models. Further study in animals will contribute to a more informed, comprehensive, accelerated and ultimately impactful suicide research portfolio.

KEY WORDS

Suicide, Aggression, Irritability, Helplessness, Impulsivity

INTRODUCTION

Suicide nowadays is a complex public health problem with lots of global importance. Suicidal behaviour significantly differs between genders, different geographical regions, age groups, sociopolitical settings, suggesting etiological heterogeneity. [1]. Suicide is defined as an act of intentionally terminating one's own life. According to World Health Organization (WHO) almost one million people die by suicide every year worldwide, representing an annual global mortality rate of 16 per 100,000. In the United States alone suicide claims over 32,500 lives annually. Along with mortality rate due to suicide, suicide attempts are even more prevalent. It is estimated that both mortality and attempts are twenty-fold more frequent in the general population. [2]

NEUROBIOLOGY OF SUICIDAL BEHAVIOUR

Serotonin (5-HT) is found to be greatly involved in cognitive and behavioural functions including suicidal behaviour. Concentration of 5-HT and 5-hydroxyindole acetic acid (5-HIAA) in Cerebrospinal fluid (CSF) plays a key role in suicidal behaviour. It has been previously reported that low CSF-5-HIAA concentration might result in an increased impulsive and violent behaviour [3]. Also, it is reported that dopamine is directly related with aggressive behaviour and some researchers found that increased dopamine concentrations in brain may be related to violent suicidal attempts or related behavioural symptoms [4].

MODELING OF SUICIDE-TRAIT-RELATED BEHAVIOURS IN ANIMALS

Animal model is any experimental paradigm that is developed with an intension of studying or correlating with human condition; however, there exist no perfect

animal model which can cover all the aspects of clinical situation concerning any of the psychiatric disorder [5]. The preclinical animal models that are developed for the study of suicidal ideation are based on the several behavioural traits in humans that can be successfully modeled in animals [6]. Study of the results from various behavioural traits in animals can provide a starting point for further studies and predictions. Following are the behaviour traits that are actually associated with clinical suicide.

AGGRESSION

Aggression belongs to the natural behavioural repertory of virtually all the animal species and can be considered as a highly functional form of social communication aimed at active control of the social environment. It is characterized by a set of species-specific behaviours performed in close interaction with opponent [7].

Resident intruder paradigm

The intruder animal in the paradigm shows defensive behaviour in response to the offensive attacks by the resident. This paradigm therefore also allows to study defensive behaviour and social stress by using the intruder animal as an experimental animal [8].

Procedure

One week prior to testing, the resident male and the female are housed together in the home cage at least a week before the testing. One hour before the test, remove the companion female from the residential cage and introduce unfamiliar male into the home cage of the resident at the start of the test. For the expression of the full offensive behavioural repertoire, 10 min duration is usually sufficient for a test. For the purpose of standardization, one can consider continuing recording for the period of ten minutes after the first attack.

After completion of the test, remove the intruder male and determine in the duration and frequency of the following behavioural parameters:

1. Attack latency
2. Move towards
3. Social exploration
4. Ano-genital sniffing
5. Rearing
6. Lateral threat
7. Upright posture
8. Clinch attack
9. Keep down
10. Chasing behaviour
11. Non-social explore
12. Rest or inactivity
13. Attack biting.
14. Wrestling
15. Submission latency
16. Move away
17. Flight
18. Freeze

Social behaviour in dog

The dog has been suggested as a suitable model species for several forms of human social behaviour especially for human psychiatric conditions [9, 10]. To carry out a complex analysis on dog aggression, it is necessary to have a precise description at the behavioural level. To assess dog temperament, including aggressive behaviour a number of tests have been developed [11]. Most of these behavioural tests comes from the applied field and are particularly concerned with the selection of shelter dogs for reintroduction to society [12].

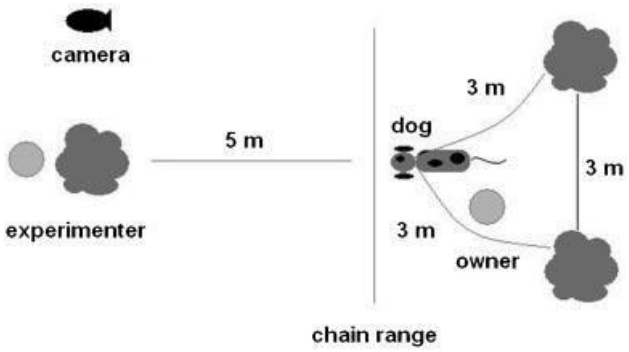

Fig. 1- The schematic figure of the test area.

Method

A total of 73 adult pet dogs participated in the test. We found 47 dogs that, already bitten to a person at least once in their lives. These "biter" dogs were further divided into two sub groups, one containing dogs that had bitten only one time during their life (OB group, N=22), and the other containing dogs that had bitten on more than one times (MB group, N=25). OB and MB groups did not differ regarding sex, age, and breed-group. Dogs in the third group, non-biter group so as to have a counterbalanced sample to that of the OB and MB. The individuals in the third group had no biting history (NB group, N=26).

Procedure

The test series consisted of five tests in a fixed order. The reason for using a fixed order was twofold: The first test was expected to obtain less aggression than the others and our main aim was to characterize the overall aggressive response of the dogs. During tests 1 to 4, dogs were tethered to two trees (located about 3m from each other); with 3m-long light chains in a V shape (see fig.1). This type of leashing prevents the dog from making semi-circular movements but allows it to move forward and backward, providing the possibility to avoid any stimuli during the test. Without moving or speaking the owner stood one meter away from the dog.

The owner put the dog on a leash in test 5. The duration of each of the five tests was between 30 and 60sec and the tests were carried out with only breaks of 5-10sec. Two unfamiliar female experimenters (S1 and S2) participated in the test series. Test 5 was performed by the owner. S1 used an artificial hand in test 1 and 2. It was a very natural-looking model of a hand, made of plaster, and covered with a glove. To hide the hand of the test-person, the artificial hand could be operated by a stick and covered with a sleeve.

Test 1- Friendly greeting:

S1 approaches the dog in normal walking speed while speaking in a friendly manner to the dog and maintaining eye contact with it. She stands 1m long from the dog. Then, she calls the dog by its name, steps closer if the dog approaches her without showing any sign of aggression and strokes it gently on the head with the artificial hand. S1 continues repeating the dogs' name for 30sec even if it shows aggression or avoid she, but she never goes closer than the chain range.

Test 2- Take away bone:

For this test we use a bone attached to a string. S1 gives the bone to the dog to chew it while she holds the end of the string. The bone is always positioned a few centimeters inside the chain range, so that the dog can choose either to approach the experimenter and the bone or to avoid them. If the dog is motivated to chew the bone, then after 5sec the experimenter strokes the dog's head with the artificial hand while talking to it quietly (5sec); then she reaches towards the bone, puts the hand on the bone and says "Give it to me!" then without saying anything holds the artificial hand on the bone(5sec); finally, she takes away the bone from the dog by pulling the rope with her other hand while the artificial hand remains on the bone pretending that she is pulling the bone with it. The test is terminated if the dog (a) tries to attack S1, (b) allows her to take the bone away, or (c) is not motivated to chew the bone.

Test 3- Threatening approach:

S2 approaches the dog slowly, slightly leaning ahead, and staring into the dog's eyes (Vas *et al.,* 2005). The test ends when the experimenter reaches the chain range or when the dog reacts with aggression (growing, snarling, snapping) or avoidance (moving away from the experimenter).

Test 4- Tug-of-war:

S1 tries to make the dog play tug of-war using a 40cm long rough fabric rag. The test is terminated if the dog cannot be motivated within 1min. With motivated dogs, S1 plays tug of war intensely but not aggressively. After a 20-sec-long play-session, S1 asks for the rag and takes it away by pulling after a 20-sec-long play-session.

Test 5- Roll over:

Preceding the test, the owner puts the dog on leash and puts a muzzle on it as he/she normally does before walks. The owner gently makes the dog lay on its back (so that the dogs' legs do not touch the ground) and attempts to keep the dog in this position for 1 min total. The owner is instructed not to force the dog physically to lay on its back, but (s) he is allowed to hold it gently even if the dog tries to stand up. After the tests, the owners were asked how often their dogs behave aggressively towards strangers (15 score) and towards the owner/family members (5 score). All tests were video-recorded by the non-tester experimenter for analysis [13].

Tube dominance test

The tube dominance test assesses cognition in rodent models of CNS disorders, particularly social dominance through the measurement of aggression. Subjects of different genotypes are released into opposite ends of a clear, narrow tube. The animals interact in the middle of the tube; the more dominant animal will show greater aggression and force its opponent out of the tube. When one animal has all four paws out of the tube, it is declared the loser while the animal remaining inside the tube is the winner, ending the match. The number of wins is reported as a percentage of total number of matches. The Tube Dominance Test is useful for identifying deficits in social interactions in strains of transgenic mice and evaluating novel chemical entities for their effect on cognition and social behaviour.

IRRITABILITY

Irritability, defined as a feeling state characterized by reduced control over temper [14]. It has been described when the animal becomes wild and/or restless in response to a tactile or auditory stimulus, and it has more recently been defined as an extreme reaction to relatively minute stimuli [15, 16].

Resistance to capture or attempts to struggle while being restrained

Many of the tests used to measure irritability involve assessing rodent struggling behaviour in response to human handling. As a response to moderate restraint applied by the handler, a mouse will either exhibit irritated response. The extent and duration of struggling behaviour is used to measure irritability [5].

Procedure

Male Sprague-Dawley rats weighing between 225-250 g were individually housed in plastic tub cages with ad libitum access to food and water. The housing room was on a 12:12 l: d cycle with lights on at 0600h. Animals were given a 5-7-day acclimation period prior to the beginning of experimentation or surgery and were briefly handled during this period. All stress experimentation took place between 0800 – 1200h.

Stress paradigms

Restraint: Animals were placed in open-ended Plexiglas cylindrical restrainers measuring 6.7 cm in diameter and 22.3 cm in length and placed in a clean cage with bedding which held the restrainer in place. Restraint lasted for 30 minutes/day, at which point animals were returned to their home cage. Immediately after the last restraint exposure (day 5 or day 8, depending on the experiment) animals were decapitated and trunk blood collected for ACTH and corticosterone analysis [17].

Forced swim: Acute and repeated forced swim animals were placed in a glass chromatography jar (18" high × 8.75" outer diameter) filled two-thirds full of water measuring approximately 25°C. Rats were swum for 15min/day, a length of time allowing some comparability to the effects of 30 min stress while also being short enough for daily exposure to be tolerated. To Animals given a single and acute forced swim exposure and decapitated immediately after swim and trunk blood was collected for analysis of ACTH and corticosterone [17].

Responsiveness to uncomfortable stimuli

These paradigms measure irritability as the responsiveness of an animal to uncomfortable stimuli. In these paradigms, an uncomfortable stimulus is given (e.g. a puff of air blown sharply through a straw onto the back of the animal's neck) and the animal's response is measure. Animals that exhibit enhanced reactivity to the stimuli are considered to display irritable behaviour [18].

IMPULSIVITY

Impulsivity is defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to themselves or other. Measuring impulsivity in the laboratory is a daunting task as it is a diverse behaviour, covering a variety of phenomena that may have independent biological mechanisms [19].

5-choice serial RT task (5-CSRTT)

This method used to assess impulsivity. An animal is trained to detect when a light comes "on" in one of five holes located in a panel. When it introduces its snout into the illuminated hole its behaviour is reinforced. A premature response occurs when the animal introduces its snout into a hole before the signal light comes "on"; this is judged animal impulsive response. Non-responses occur when a hole lights up, but the animal takes no action, and are classified as signs of attention failure; hence, this method can also be used to assess sustained attention [20].

Wait-to-Go-Signal Task

Impulsivity is defined as the failure to inhibit a pre-potent response. In the present study, this type of impulsivity was assessed on the basis of anticipated

responses to a Go-signal tone. For this application only one bridge was used, and panels were placed on the platforms to block transit from area A to C and from area B to D. The bridge width was 3.0 cm, as our experience in several training tests with bridges of different dimensions showed that 3-cm bridges can be crossed without difficulty [21].

Training procedure:

Initially, a rat was placed on platform A and trained by shaping to cross toward platform B, where it would obtain a 45-mg pellet as a reinforcer. The pellet was available in a container placed on platform B. The acquisition criteria for this behaviour required performing at least 15 consecutive crossings from platform A to B with a latency response 10 seconds timed from the moment at which the rat was placed on platform A. This criterion was usually satisfied in two days. On the following day, a tone (350 ms, 4 kHz, 40 dB) was generated by the interface one second after the rat was placed on platform A, and only the crossings that occurred after the tone and with a RT 2 seconds were reinforced. This training phase consisted of one daily session of 60 trials designed for the rats to establish a relation between tone, crossing, and reinforcement. After two days in this condition, and regardless of the rat's performance, the tone was presented 2 s after placement on platform A. As in the previous phase, only the crossings that occurred after the tone and with a RT 2 seconds were reinforced, as they constituted correct responses. The learning acquisition criterion for this task was 32 correct responses of 60 trials in each session. Thirty-two was the mean 2 standard deviations of the correct responses obtained on the first day of exposure to 2 s of tone delay presentation.

Testing procedure

Once this criterion was achieved, the rats were evaluated for two additional days in this phase under the same conditions. In the two phases that followed, the tone was presented randomly at 2-3 and 3-4 seconds, respectively, and each phase lasted 3 days, regardless of the rat's performance. After each crossing, the rats remained on platform B for 10 seconds, whether they had received a reinforcer or not, before the next trial began. The following measurements were considered in this task:

1. **Correct responses**: Crosses occurring after the tone and within a RT 2 s.
2. **Omission responses**: Remaining on platform A for more than 2 s after tone emission (in attention measure).
3. **Anticipated responses**: Starting to cross before tone emission (impulsivity measure).
4. **Reaction time for correct Responses:** Time elapsed from tone emission to commencement of crossing within 2 s.
5. **Crossing latency for anticipated responses:** Time elapsed from the moment the rat was placed platform A to commencement of crossing before tone emission.

Delay-discounting paradigms

One of the most successfully utilized measure of impulsive behaviour is intolerance to delay- of-gratification, or delay-discounting, which is the function by which a reward is subjectively devalued by a delay to its delivery. Impulsive choice is defined as the selection of the smaller immediate reward. In delay discounting paradigms, the subject essentially chooses between responding on one lever which leads to a small reward and another which leads to a large but delayed reward. Such tasks can be divided into "systematic" tasks, where the experimenter varies the delay to different sized reinforcers and then measures the number of choices made of the large reward at different delays or "adjusting" tasks in which the behaviour of the subject determines the delays sampled [22].

HOPELESSNESS/ HELPLESSNESS

Hopelessness has argued against this belief and proposed that a person's hopelessness can be objectified by denning it in terms of a system of negative expectancies concerning himself and his future life. Hopelessness has been identified as one of the core characteristics of depression and has been implicated in a variety of other conditions such as suicide.

Learned Helplessness Paradigm

Learned helplessness paradigm is based on the assumption that for aversive stimuli (foot shock) animals have a normal tendency to escape, but when the stimulus is inescapable they will eventually stop trying for escape. The paradigm is divided into three phases: induction, screening and avoidance test. Induction: An animal is given several foot shocks from which it cannot escape. Shock intensity and the number of trials are varied. The duration between each shock trials is randomized, and, in most cases, the shock is

associated with a conditioned stimulus. Screening: The test is mostly conducted a day after induction, where several escapable shock trials are given. The animal is regarded as helpless if still it fails to escape the shock and if the animal makes an attempt to successfully escape the shock, it is deemed to be 'non-helpless'. Duration between trials is randomized, although shock intensity and time window allotted for escape can vary. Avoidance test: After several days of screening, 'helpless' animals are given an active avoidance test consisting of several escapable shock trials. If an animal makes an attempt to escape a set number of trials, it is considered to be 'recovered', if it does not escape, it is considered to have 'learned helplessness' [5].

CONCLUSION

Animal models can be widely used for investigating behavioural traits that shows a strong correlation of suicide in clinics. Though it is a challenging task to develop the animal models of suicide, certain main risk factors that are the indicatives of suicidality, can be modeled in rodents, including aggression, irritability, impulsivity and passive avoidance. These traits can be considered as the main traits correlated with suicidal ideation.

REFERENCES

1. Turecki G, Brent DA, Suicide and suicidal behaviour. Lancet (London, England), 387(10024):1227-1239, (2016).
2. Gvion Y, Apter A, Suicide and suicidal behaviour. Public Health Reviews, 34(2): 1-17, (2012)
3. Almira O, Katja V, Neurobiological aspect of suicide. A review of low cerebrospinal 5- hydroxyl indole acetic acid concentration and prediction of suicidality, 1-25, (2007)
4. Erik R, Lindstro M, Lil Tra SB, The role of dopamine and serotonin in suicidal behaviour and aggression. Prog Brain Res, 172: 307-315, (2008)
5. Malkesman O, Pine DS, Tragon T, Austin DR, Henter ID, Chen G. Animal models of suicide-trait-related behaviours. Trends Pharmacol Sci, 30:165-73, (2009)
6. Blanchard RJ, Wall PM, Blanchard DC. Problems in the study of rodent aggression. Horm. Behav, 44 (3):161-170, (2003)
7. Coppens JM, Boer CM, Buwalda SF, Meerlo B, The Resident-intruder Paradigm: A Standardized Test for Aggression. Violence and Social Stress. J. Vis. Exp, 77:1-13, (2013).
8. Toth L, Gacsi M, Topal J, Miklosi A., playing styles and possible causative factors in dog's behaviour when playing with humans. Appl Anim Behav Sci., 114: 473-484, (2008).
9. Vas J, Topal J, Gyori B, Miklosi A, Consistency of dog's reactions to threatening cues of an unfamiliar person. Appl Anim Behav Sci., 112:331-344, (2008)
10. Mornement KM, Coleman GJ, Toukhsati S, Bennett PC, A review of behavioural assessment protocols used by Australian animal shelters to determine the adoption suitability of dogs. J Appl Anim Welf Sci.,13: 314-329, (2010)
11. Poulsen AH, Lisle AT, Phillips CJ, an evaluation of a behaviour assessment to determine the suitability of shelter dogs for rehoming. Vet Med Int., 523781, (2010)
12. Klausz B, Kis A, A Quick Assessment Tool for Human-Directed Aggression in Pet Dogs. Aggress. Behav, 9999: 1-11, (2013)
13. Snaith RP, Taylor CM, Irritability: definition, assessment and associated factors. Br. J. Psychiatry, 147: 127-136, (1985)
14. Suzuki M.-S. LuH. Motegi T. Yoshii, M. Misawa, Genetic differences in the development of physical dependence upon diazepam in Lewis and Fischer 344 inbred rat strains. Pharmacol Biochem Behav, 43(2): 387-393, (1992)
15. Einat H, Modelling facets of mania-new directions related to the notion of endophenotypes. J. Psychopharmacol, 20(5): 714-722, (2006)
16. Grissom N, Kerr W, Bhatnagar S. Struggling behaviour during restraint is regulated by stress experience. Behaviour Brain Res, 191(2): 219-226, (2006)
17. Markesan OZ, Laura BT, Jessica Oz, Joseph TM, Traumatic Brain Injury-Modeling Neuropsychiatric Symptoms in Rodents. Front Neurol, 4: 157, (2013)
18. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC, Psychiatric aspects of impulsivity. Am. J. Psychiatry, 158:1783-1793, (2001)
19. Pitna K, Inha C, A Simple Behavioural Paradigm to Measure Impulsive Behaviour in an animal Model of Attention Deficit Hyperactivity Disorder (ADHD) of the spontaneously hypertensive rats. Biomol Ther, 125-131, (2012)
20. Dalley JW, Theobald DE, Pereira EA, Specific abnormalities in serotonin release in the prefrontal cortex of isolation-reared rats measured during behavioural performance of a task assessing visuospatial attention and impulsivity. Psychopharmacol, 164: 329-340, (2002)
21. Jorge J, Patricia M, Assessing Impulsivity in Prepubertal Male Rats: A Novel Device and Method to Assess Motor and Cognitive Impulsivity. Exp Clin Psychopharmacol, 21(4): 315-322, (2013)

22. Winstanle CA, Eagle DM, Robbins TW, Behavioural models of impulsivity in relation to ADHD: Translation between clinical and preclinical studies. Clin. Psychol. Rev, 26: 379-395, (2006)

***Corresponding Author:**
Padmaja Kore*
Email: **padmaja.kalshetti@gmail.com**