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Animal Models Receptive to Antidepressant Treatments: A Review

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Abstract

Background

Depression is one of the most leading disorders in the world. To study its pathways of occurring we use different types of animal models. To find its pathophysiology different types of species different models are used. In this review all method use m induction of depression are elaborated.

Method

Review of literature is conducted on different types of data bases such PubMed, eleviser etc.

Result

Different sources suggests that there are various number of ways by which depression can be induced. Different factors such as by changing the environment, chemical methods it is possible to study the consequences of depression.

Conclusion

None of the model of the depression is best in itself to study the depression. Each one has it own advantages and disadvantages. So in order to understand pathophysiology of and for its better cure new models must be developed.

Keywords: Depression, mental disorder, models, stress, deprivation.

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Introduction

Health word is of Gennanic origin which is means 'whole' 'a thing complete in itself. It is defines as state which is free from illness. It is physical, social and mental well-being not only free from disease condition and infirmity (Harald Brüssow 2013)(Yadav & Verma 2019).

Health can be divided mainly into two types of physical and mental health. Physical health is condition which is free from disease condition. Mental and psychological well — being is mental health. Following are facts related to mental health.

l . Mental, behavior, neurological disorders are common to all countries of world and cause extensive suffering. People who are suffering from these types of disorders face poor quality of life, social isolation and mortality. These disorders increase burden on economy.
2. Millions of people are suffering from mental health, behavior, neurological disorders about more than 300 million people suffers from depression (WHO 2017), schizophrenia 25 million, 50 million people suffer from epilepsy and 24 million from Alzheimer and other dementias.
3. Mental conditions affect and affected with the other conditions tuberculosis, cancer, HIV AIDS.
4. Low and middle income countries spent less than 1% on mental health(WHO Depression and Other Common Mental Disorders,2017)(Amrinder & Sharma, 2016).

Depression is one of the leading mental disorders in world. Depression is generated due to stressful events in life so many factors are related with depression. In terms of science various hypothesis of depression are given. Monoamine hypothesis, HPA axis, neurotropic factor hypothesis, inflammation hypothesis. Some other hypothesis which recently added are GABA or glutamate role in depression(Fekadu et al., 2017; Hasler, 2010). All these are linked with the depression. Based upon these theories many drugs are come in market to counteract depression. The first drug iproniazid is show antidepressant effect. This act on the MAO which control the concentration of the monoamines in all body. This give rise to the first class of chugs known as MAO inhibitors. This leads to generation of monoammes hypothesis Hypothesis help in developing various thugs, includes serotonin reuptake inhibitors, nor adrenaline reuptake inhibitors, down regulating of beta, and nor aderanline and serotonin reuptake.

Genesis of depression models of animals

Animals are used to reproduce disorders in order to discover new drags. By usmg animal we generate disorders such as Parkinson's, Alzheimer, epilepsy and depression etc. Animal in which these disorders are induced show similar behavior as by human being. Animal models are only able to generate symptoms of depression via these ammal models we are not able to study etiology of depression (Duman, 2010).

Depression occurs due to neurotransmitters imbalance. Major depression is disorder which is characterized by symptoms which include lost of interest in sexual activities and other activities

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which pleasure a person defined by DSM IV. Thoughts of suicide and other symptoms which if remain for 2 week than person is said to be depressed. Discovery of behavioral drugs use in depression is occurs by chance. The TCA inhibit reuptake of neurotransmitters to treat depression which include dilig such as impiramine first it is use in schizophrenia patient to claim them. For treatment of tuberculosis anti-tuber drmg such as iproniazid, isoniazid improvesthese behavioral disorders. Drug such as reserpme used to treat high level of blood pressure cause depression in person by lacking of monoamine in person. Anti-tubular drags makes person active by increasing level of monoammes. This hypothesis is postulated that in depression level of dopamine and other neurotransmitters decrease. Due to these depression is occurs(McArthur & Borsini, 2006).

Validity of animal models of depression

For evaluating models of depression following criteria is established.

1. Face
2. Etiological
3. Constructive
4. Predictive

Face: Symptoms of depression arises should be similar to human being. It is just a basic idea to valid the model of depression. Behavioral changes of depression are compares with human being.

Etiology: What is reason behind depression by which factors depression occur. Models is able to find cause of depression it is valid.

Construct: It relates to causative and symptom of depression. It also shows similar pathology of depression m such as neurotransmitter levels other parameters in depression. This similarity has shown high validity model, depression.

Predictive: Prediction of anti-depressant on human same effect as on animals(Abelaira et al., 2013; McArthur & Borsini, 2006).

End point of behavior in depression models: Core symptoms of depression include anhedonia, depressed mood, alternation in appetite and weight. Other symptoms like anxiety, social withdrawal(Hasler et al., 2004) can be easily induce in animal so various test performed to evaluate these symptoms. It is difficult to access anhedonia than depressed mood. Depressed mood can be expressed by social withdrawal, slow gait shows psychomotor retardation(Levy & Dubois, 2006). Some symptoms such as excessive guilt, worthlessness felling, thoughts of suicide and death arenot seen in animal model. This behavioral difference is existing between human and animal. In terms of behavioral end point in animal models only some behavioral points can be observe.

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Behavioral points in models of depression

Anhedonia: Anhedonia can be access with the help of food and solutions. Intracranial threshold is another method by which it can be accessed which is more complex (Cryan et al., 2003) For example a animal is have two choice for drinking water one is sucrose water another is simple water. For eating two types of cookies there one is simple and other is chocolate cookie. Normal animal who is not suffering from depression give preference to palatable food which is less in animal show anhedonia behavior (Klein, 1974). We can access anhedonia by measuring sexual behavior. For this a female animal is requires which undergone removal of ovary.

Despair: To evaluate this parameter we use force swim test and tail suspension test. Both types of test animal are placed in uncomfortable situation. First they try to escape from this situations. After straggling for long time animal become immobile. Antidepressants dlllgs increase the motions m animals to escape from situations which arise. This test is now a golden point to test molecules for depression (Porsolt et al., 1977).

Apathy: Deficiency in goal directed behavior is known as Apathy(Levy & Dubois, 2006). To find this type of behavior we use following points social withdrawal, not able to make nest, reduce interest for novel objects(Cathomas et al., 2015). Two factors of MDD animal models were measured: Nest building and groommg, either with a deterioration of the coat and with the splash test. The spontaneous activity must be measured in parallel, as a decline in activity can have an unspecified effect on spontaneous attitude. In short, the measure of the degradation of the coat status consists of the evaluation of the condition the fur on seven parts of a mouse's body: when the animal is nervous and can indicate degradation of the coat condition (Pretended or dirty coat). Splash test is composed of water splashing on animal and then test for groommg behavior m animal induce.

Hopelessness: It is predicted with the help of learned helplessness. In this one group of animal is placed in the box from which animal not able to escape and electrical shock is applied. Another group of animals are placed in box from where animal can able to escape. When animals who are previously subjected to shock in box in which animal not able to escape out then placed in box from which escape is possible they show learned helplessness fail to escape from box(Maier & Seligman, 2016).
Anxiety: With the help of so many devices we can predict the anxious behavior of animal(Gould et al.,2009) By putting animals in new environment this behavior can be easily accessed. For this purpose we can use elevated plus maze, open field test, and light and dark mode exploration.

Abnormalities in behavior of eating disorders: Patients suffering from depression are show change in food habits either weight of person Increase or may be decrease(Hasler et al., 2004). Change in weight can be predicted by measuring weight of animal in regular intervals of time. In order to measure food habit measure amount of food given to animal then find amount of food eaten by animal. In this way we can check food taking habits of animals.

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Sleep disturbance: Depressed animal suffers from sleep disturbance also. To measure sleep disturbance rapid eye moment can be use. Diurnal ambulatory behavior is also affected in case of sleep disturbance which can reflect this behavior(Ding et al., 2018).

Psychomotor retardation or agitation: Retardation and agitation reflects impairment in general activity of person (Vollmayr & Henn, 2003). Exploration of new environment and activity of animal in cage reflects this type of impairment(Dadomo et al., 2011). To find abnormalities in local motor activity we can use open field test and plus maze test. Force swim test also use to evaluate this type of impairment(Overstreet & Wegener, 2013)

Irritability: This is core factor present in children and young people suffering from depression(Kovess-Masfety et al., 2013). In melancholic depression anger and irritation are two factors in diagnosis of depression, women who is suffering from postmenstrual dysphoric disorders also show this types of symptoms(Hantsoo & Epperson, 2015). Resident — intruder test is use to measure irritability(Schneider & Popik, 2007a). To evaluate this test is performed known as buried marble. In this test sand marbles (nine marble) are place in cage more marbles are buried by animal more is abnormal behavior of animal. This behavior can treated by SSR1(Schneider & Popik, 2007b).

Cognitive impairment: In depression learning ability is also gets affected. Cognitive impairment is one of most important feature in major depression disorder. In current dlllgs are focusing only to treat mood. With help of social and object identification test we can test memory of animal (Leger et al., 2013) In SRT test time passed with new comer is evaluated, in ORT time spent with new object is measure. Morris water maze test is use to measure spatial memory and cognitive memory m case of depression (Darcet et al., 2014)

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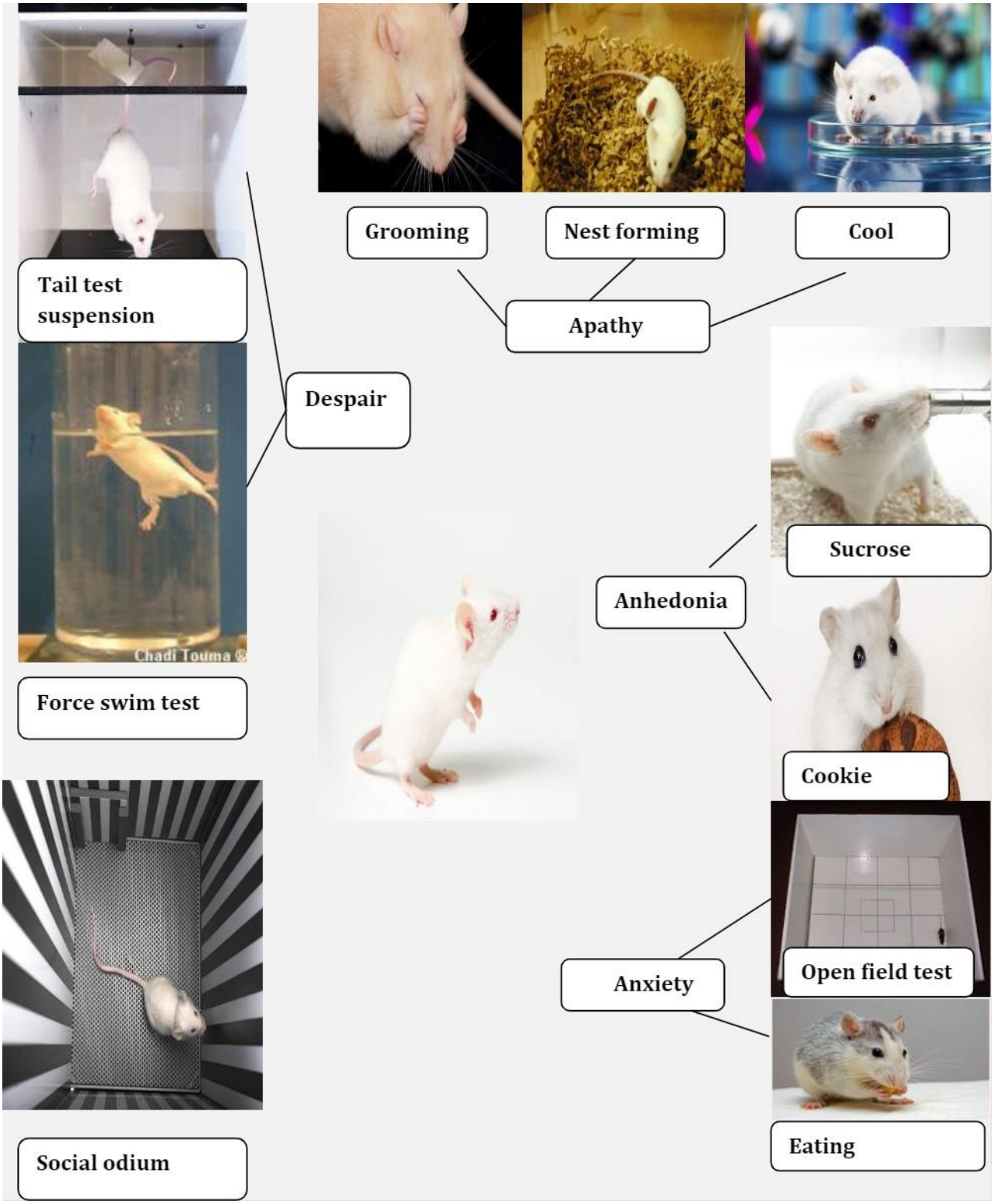

Neurochemical models: 1960 is a time during which animal models of depression based on neurochemicals are introduced and refined.First model based in neurochemical is to antagonize

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Fig 1: Behaviour of animal observed in depression

the activity of resperme which decrease level of central monoamines. This model makes a difference between antidepressants and other psychotic thugs.Resrpine induce hypomobility, bradycardia, diarrhea, all these effects are reversed by TCA and monoamines oxidase inhibitors. Using yhombine and clonidine the antidepressant activity of chugs are also studied. Yhombine is show antagonism activity at 2 receptor increase healt rate by increasing the release of noradrenaline. These effects are increased by antidepressants such as TCA, MAO inhibitors and serotonin reuptake inhibitors. A drag called parachloramphetamine which directly affects serotonin system its level gets decreases. Due to decrease in level hypothermia is occurs which is reversed by antidepressant. Models based on neurochemical are used to investigate receptors involved in pathophysiology of depression.(McArthur & Borsini, 2006)

Models based on stress: These models are based upon applying stress to animals stress may be mild or chronic.

Chronic mild stress: It is most validated model of depression ((Katz, 1982). In this model animal is subjected to stress several times is a day in unpredictable manner. Chronic mild stress induces depression behavior in animals such as reduction m investigational behavior, sexual activity, aggressive behavior and locomotor activity. Chronic mild stress is introduced by Katz et al. Initially for in this model animal is subjected to electric shock, immersion to cold water, light and dark cycles. All these stressors increase level of corticosterone which causes depression. CMS major drawback is time consumption, more labor and space is required. It is difficult to reproduce in new laboratory.

Acute stress: In this model animal is subjected to inescapable situation in a box consists of grid electric shock is applied from which animal is not able to escape. When animal is gain placed in same situation from which animal can able to escape but fails. This situation is known as learned helplessness. On repeating this inescapable situation leads to activation of I-IPA axis in brain. This leads to depression like behavior in animal(Carmichael & Lockhart, 2012). In learned helplessness models animal face weight / appetite change, sleep change, cog native impairment, loss of synapse in hippocampus region of brain, libido. This all changes are reversed by using antidepressants such as TCA, serotonin reuptake inhibitors and monoamine oxidase inhibitors. These dlllgs show their effect after two to three days of starting treatment. Changes in level of neurotransmitters and number and sensitivity of receptors also gets altered in the learned helplessness. High level of glucorticoids is also present m animal which can also see in human being. In this model depression like symptoms are not persist for the longer period of time(Abelaira et al., 2013).

Early life adversity/ maternal deprivation: Early life experience which not in favor of animal or person. Represent risk factor for development of major depression disorder. Early separation from maternal is stressful event which leads to effect behavior and biological phenotype of offspring. Due to stress conditions I-IPA axis impairment occurs. Separation of rodents from maternal mimic same stressor which is faced by a person due loss or ignorance of parents in early life, we can easily

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find pathophysiology of depression by this model. Maternal separation is use to study early life adverse effect on neurobiology(Abelaira et al., 2013).

Sleep deprivation: Sleep is requires for good health. For homeostatic it is necessary, if regular and proper sleep is not taken by animal and a person then it act as stressor to animal and person that stimulate and effect mood. Sleep deprivation is not established as model but according to study it alters the pathway associated with stress. Sleep deprivation in animal leads to increase level of mRNA related to proinflammatory factors. Level of corticosol increases in animal. After 72 hours of sleep deprivation ammal increase oxidative stress in hippocampus of brain. After 96 hours of sleep deprivation animal impairment seen in cognitive behavior. Learning capacity is also getting affected. Due to this there is change in level of neurotransmitters dopamine and serotonin leads to change behavior. Anhedonia is also observed in case of sleep deprivation. But this models meet only some factors of validity of models of depression (Abelaira et al., 2013).

Social defeat: In this test animal is placed in other another cage. In this cage aggressive animal is present for ten minutes. Already present animal in cage attack animal some time animal under test get injured. For rest of the day test animal is m visual, olfactory and auditory contact with aggressor animal. For ten days this process is repeated for every 60 seconds, each time new animal is faced by test animal. In this type of model prefrontal cortex affected, hyperactivation of amygadla. In this proinflammatory factors are also increase and level of neurotropin decrease. To treat social defect SSRIs and ketamine used(Planchez et al., 2019).

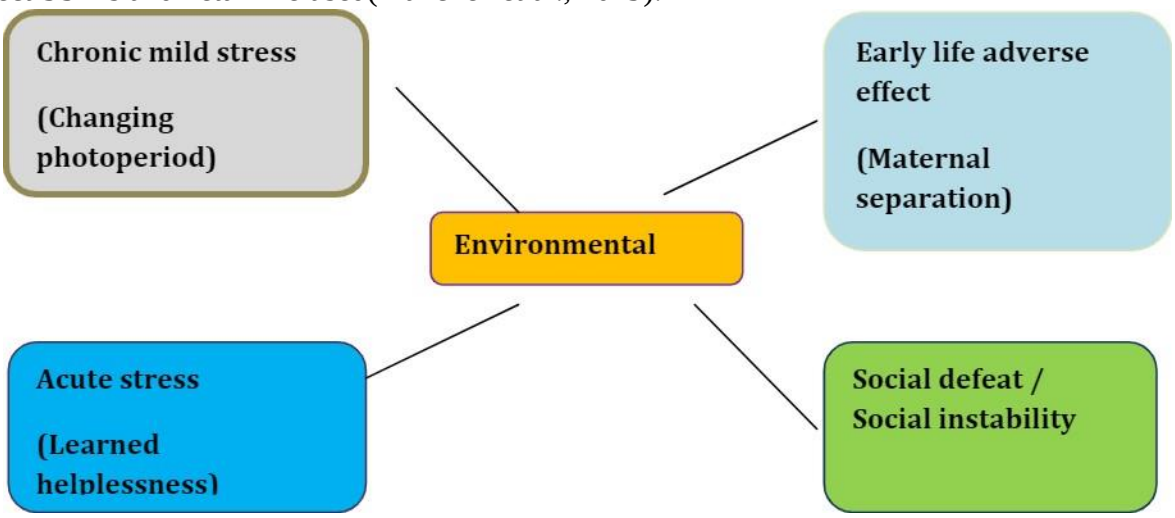

Figure2) Depression due to change in environment

Models based upon biological causation: Depression leads to alternations of biological factors in body. In depression activation of I-IPA axis, increase level of corticosteroid, proinflammatory cytokines, level of neurotransmitters such as dopamine, noradrenaline, serotonin. By inducing these biological changes depression take place in animal.

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Biological changes by injury olfactory bulbectomy: Bilateral olfactory bulbectomy can change level of neurotransmitter, alter endocrine, behavior and immune system response m body. This Injury munc same changes as occurs in human being. Olfactory system of rat is a part of limbic system which forms hippocampus and amygdala that involves in regulation of mood. This injury leads to degeneration of neurons in various parts of brain include prefrontal cortex, hippocampus. These factors affect serotonin and noradrenaline system of brain. This model increase exploratory behavior of animal and locomotor activity. But it affects sexual behavior and activity of animal generates anhedonia behavior. This model show predictive validity of antidepressants. Antidepressants reverse all the changes cause of these model at physical and t al., 2013)molecular level in body(Abelaira et al., 2013).

Table 1) Models of depression (Abelaira et al., 2013)

Environmental Change	Features
Chronic mild stress	Decrease sexual potency, aggressiveness, locomotor activity, increase corticosteroid level in plasma, anhedonia
Learned helplessness	Weight loss, alternation in sleep patterns, loss of spine synapses in hippocampus, decrease in norepinephrine and serotonin and high level of glucocorticoid
Maternal deprivation	Level of glucocorticoid , decrease in neurtrophins like BDNF and neurotropin-3
Sleep deprivation	Increase level of pro inflammatory cytokines and cortisol
Changing photoperiod	Anhedonia behavior, Increase motor activity and level of corticosterone decrease BDNF in hippocampus
Injuries	Features
Olfactory bulbectomy	Changes in endocrine , behavioral , immune system and neurotransmitters that cause depression decrease in sexual activity , degeneration of neurons in hippocampus
Chemical manipulations:Stimulation of immune system	Features
Lipopolysaccharide	Neuroinflammation, cognitive impairment, micoglial activation, neuronal cell loss, level of TNF-ff,
	interleukin-lß, prostaglandin E2(PGE2),nitric oxide increased, increase COX-2, iNOS,

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Interleukin-4	Inhibits production of TNF and IL-I stimulates B cells
Interferon- (INF-u)	Induction of viral resistance natural killer cell activation Macrophage activation
Interferon(INF-Y)	Macrophage activation T cell differention

Change in biology with chemicals: Chemicals can induce changes in immune system and induce depression. Several studies show that in depression there is alternation in immune system. Inflammatory mediators has role in depression. These affect level of neurotransmitters, neurotropins. Cytokine is a inflammatory mediator has different role in our body. In depression level of IL-6,IL-10 increases. Antidepressants drugs normalize the level of these inflammatory mediators. Administration of endotoxin such as lipopolysaccharide a bacterial endotoxin induce the symptoms of depression. It is administer at different doses to induce depression dose range is from 0.5 — 0.83mg/kg(Planchez et al., 2019). Lipolysaccharide induce inflammation related to major depression. Inflammation alters behavior and increase preference to simple water.This behavior is due to increase level of inflammatory factors in brain. Proinflammatory increase oxidative stress in brain affect neuroplasticity requires for learning and memory. Neuroplasticity level decrease due to decrease in level of BDNF a neurotrpin requires for pasticity in brain. Level of corticosterone affects limbic and monoamine system of brain. Tumor nacrotic factor is also involved in alternation of brain system. Antidepressant given in this condition reverse changes cause by endotoxins. Cytokines are inflammatory mediators that interact with pathways related with depression, including neurotransmitter metabolism, neural plasticity, and neuroendocrine ftnctions. Depressed patients exhibit high levels of proinflammatory mediators, such as interleukins (IL-I, IL-2 and IL-6) and tumor necrosis factor (TNF). Moreover, treatment with antidepressants has been shown to decrease levels of IL-4 in patients with depression. Neuroendocrine changes, which help determine construct validity, were also found. Treatment with the antidepressants fluoxetine and desipramm reduced anhedonia in these ammals. Interestingly, the neurobiological changes extend beyond neuroinfammation, as decreased BDNF levels in the PFC and hippocampus together.

Corticosterone administration: In stress conditions level of corticosterone increase. Increase amount of corticosterone leads to HPA activation which affect neuorgensis in hippocampus and prefrontal cortex. Corticosterine administration mimics same condition and behavior changes in brain as in case of depressed person. Induction of depression by this method shows validity. It induces neurological changes by which understanding of mechanism of antidepressant drugs is easy. Experiment reduces variability of experiment due to control dose of corticosterone.

Animal models use in for screening antidepressants

Force swim test: Forced swimming test

This test is used to evaluate anti-depressants activity. Test is given by Porsolt et al. To perform, animal is placed in container filled with water from which animal not able to exist. At initial stage of experiment mice will try to break from confinement, but after some time mice become immobile,

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it is known as passive behavior which is shown by absence of movements. Those movements are present only which are necessary for mice to remain above water level. This test is performed for both rat and mice. For mice 6 minutes exposure is done the initial 2 minutes is habituation time and last 4 minutes are test itself, which show the duration of immobility.

Tail suspension method

This test is introduced 20 years ago; it is widely used for evaluating antidepressant activity of compounds. In this test only mice are used. Short term stress is inducing in mice by suspending by tail. Mice are subjected to short term stress of being suspended by tail. Tail of mice is attached and suspended by an adhesive tape. During period of 6 minutes in which mice remain immobile is measure as depressive behavior. Antidepressants drags promote escape related behavior and decrease immobility.

Table 2) Assessment of models of depression and advantages and disadvantage

Behavior induce	MDI) behavior	Preferred Strain	Advantage	Disadvantage
Escape latency	Hopelessness	Holtzman	A depressed group which show learned helplessness other group for comparison	Various rats are requires for comparison between depressed and normal group
Force swim test(FST)	Despair	Rodents	Simple and Inexpensive a quick method to assess drug activity	Validity is weak and high variability depends on depth of cylinder, temperature
Tail suspension Test (TST)	espalr	ouse mode s	t IS Inexpensive and quick method of screenmg of dlllgs	Only nuce are tested. Results are based on motor activity Impairment
Open field test (OFT)	Anxiety/ motor activity	Mostly m rodents	A fast method to screening of drugs	It test anxiety not depression

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Sucrose preference test	Anhedonia	Mostly in rodents	Drug screening test inexpensive	Method may vary lab to lab
Early life stress	Anxiety and down regulation of BDNF expression	Sprague Dawley	Stable m Phenotype	Special handling requires is
Social defeat	Anxiety and anhedonia	Sprague Dawley	Stable m phenotype	Adult males use to evaluate
Olfactory bulbectomy	Serotonin level decreases and anhedonia	Sprague Dawley	Many neurological changes are induce that help in investing antidepressant action	It is irreversible process requires surgery for extraction of olfactory bulb
Unpredictable chronic stress	Sensitivity towards reward decreases and anhedonia	Sprague Dawley	Easy method to screen of dimgs behavior changes with time	Procedure is complex which difficult to reproduce
Chronic restraint stress	Corticosteroid level increases, CA3 pyramidal cells impairment of the Hippocampus	Sprague Dawley	Valid model for depression	Eating habits drinking habits affected
Glucocorticoid/ corticosterone	Dysregulation of HPA axis, Anxiety	Wistar	High validity	Repeated administration of corticosterone

Conclusion: For the study of depression and other disorders different models are used to induce depression. But none of model is accurate in study of depression. Different models has different advantages and disadvantages in study of depression in order to better understand this disorder we has to develop better models. The pathophysiology of depression is very complex it is not easy to minuc exactly the disorder in animal because in animals it is difficult to understand the behavior which is seen in man duringdepression. So for better treatment of depression the exploration of pathophysiology must be done.

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