BSE656 Report Group 9

"Mice are a useful model system for psychiatric disorders": For the motion

Introduction

With nearly a fourth of the human disability population suffering from them, psychiatric disorders present an urgent need for precise diagnosis and treatment. They are responsible for many differences between diseased and normal individuals, at the genetic, neuro-circuit, neurodevelopmental, neurological and behavioral levels. To move from diagnosis to a therapeutic, various experimental approaches are used. Animal models such as rodent models is one such approach that has been used for the study of psychiatric disorders.

The development of such models offers various roadblocks because it is tough to ascertain the exact molecular pathology and the etiopathogenesis of psychiatric disorders. At the same time, there are no well-defined parameters that can be used for diagnosis. Hence, the question of their viability for such studies has long been debated. While on the facet it may seem that while a great deal of time, effort and resources have been spent, the efforts have not been reproduced as major therapeutic interventions. We argue that despite these challenges, mice models help ascertain neuronal circuits responsible and various behavioral characteristics associated with each disorder due to the largely common structural and functional organization of the brain across mammalian species. Thus, their importance cannot be ignored.

The relevance and importance of mice models

- **Alzheimer's disease:** Transgenic mouse models of Alzheimer's disease (AD) have been helpful for studying amyloidosis (*building up of amyloid in organs*) (Lamb et al 1999, Schenk et al 1999, Borchelt et al 1997). Mice models have produced remarkable results which in turn helps in understanding AD better; in particular, the importance of genetic lesions and response generated to damage caused to amyloid. Using different methods, mice models that develop amyloid deposits have been successfully developed and tested for cognitive impairment using tests for hippocampal dysfunction (Dodart et al 1997, Justice et al 1997) and water maze performance (Chapman et al 1999)). Similar to neurodegeneration in humans, there is a widespread cellular disturbance and neuritic dystrophy in the vicinity of amyloid deposits.
- **Symptom correspondence:** It is not expected that an animal model like mice will completely mirror a human psychiatric disorder in all aspects. But, there is sufficient

evidence to suggest that a significant one-to-one correspondence between human and animal symptoms exists. (Some symptoms may be the same while some may be different). For example, compulsive grooming in genetically engineered mice may correspond to behavior accompanying obsessive-compulsive disorder in humans[8,9]. Thus, mere replication of genetic lesions won't produce the same effect on a mouse as that of a human.

- **Autism Spectrum Disorders (ASD) :** Researches[10,11,12,13] have independently developed mice models that have shown excellent advancement in the genetic study of Autism Spectrum Disorders (ASD). Mouse shows social interactions and observation and quantification on social behavior like sniffling body parts and male-female aggression replicate the symptoms of ASD. Researchers successfully replicated the symptoms of ASD like adherence to routines and motor stereotypes in mice.[25,26]
- **Schizophrenia and NMDA hypofunction:** Although there is no exceptionally well animal model till date for schizophrenia, there are a number of mice models that show abnormalities similar to schizophrenia[15,16]. Mice models are essential in examining the consequences of NMDA receptor hypofunction. NMDA receptors play a vital role in a number of psychiatric disorders.
- **Social defeat:** Multiple researches[17,18] produced mouse models that closely resemble the human "chronic social defeat stress". The syndrome is characterized by weight gain and hormonal activities very close to the one observed in humans. Even in one-time or intermittent "social defeat", the defeated mice experience symptoms like helplessness, hyperactivity etc which correspond really well with humans [22].
- **Social isolation:** It is really interesting to note that maternal separation at a young age and long term social isolation in mice expresses a phenotype resembled by social affective and cognitive dysfunction, corresponding to increased anxiety and aggressive behaviour [21].
- **Bipolar syndrome (Manic depression):** Not only depressive but also manic behavior (popularly known as a bipolar syndrome), has been modeled on mice[19]. Reduced anxiety (by observing mobility) is observed in this model similar to humans. This model is special also because the human manic behavior which was not known very well until now is being studied using these models.
- **Gene-environment interactions:** *DISC1*, a gene that plays a vital role in psychiatric disorders such as schizophrenia and depression is utilized to examine the interaction between gene-environment risk factors. Environmental factors most relevant to these disorders and social stress in mice are comparable to human psychiatric conditions.
- **Treatment of trauma:** Mice models for PTSD are used to test the influence of early (after 1 day) and late extinction training(after 1 month) on fear extinction after shock. It was observed that both the trainings resulted in a long-lasting reduction of fear while only early extinction led to an improvement of hyperarousal(non-associative fear memory). It

suggests that early post-shock intervention strategy can be successfully used to reduce hyperarousal post-trauma[27].

- **Similarity in developmental aspects:** One of the complications in choosing a suitable model is the difference in developmental time-points of different brain regions across the models. Mice model show significant similarity to human embryo development during the first half of the gestation period. Also, postnatal brain development is similar between mice and humans. [23].
- **Advantages of mice model over other models:** Mice models have been extensively developed and tested for numerous investigations that correlate to humans. In terms of genetic investigations, there are clear and significant advantages of mice models, for example, the availability of many inbred strains, the near-complete sequencing of the mouse genome, ease of manipulation of mice genes, etc.

  Transgenenetic and molecular biology techniques can be used to create tissue-specific knockouts and developmental stage-specific knockouts for studying the spatial and developmental aspects of the disease. Generating knockouts in mice is easier due to knowledge of genome as compared to monkeys and other mammals.
  Simpler organisms like C.elegans can be used to understand metabolic pathways and higher organisms like monkeys can be used to study behavioral correlates with the human diseased condition.

Conclusion-

Presently, mice models seem to be an indispensable approach for investigating several aspects of psychiatric conditions. Since 1960 no direct molecular level investigations on human subjects have been carried out due to ethical and practical reasons[14]. This has made reverse engineering the psychiatric disease models a difficult task in human diseased phenotypes. Additionally, mice models have the advantage of the abundance of inbred strains for studying knockout effects. Mice being a mammalian model organism, there exist significant developmental similarities between mice and human embryos. This allows for the investigation of the developmental aspects of many neurodevelopmental diseases. Although behavioral aspects may not be highly correlated with human diseased conditions, there is substantial positive correspondence between the disease models regarding some specific and characteristic behavioral attributes observed across mice and humans like socializing, etc. Molecular and neuro-circuit level investigations can be reproducibly extrapolated to the human brain in diseased conditions and this can be validated in large human datasets of these diseased conditions. Therefore, the importance of mice models cannot be outrightly rejected and the implications derived are countless.

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