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Chemical Induced Rodent Model of Autism Spectrum Disorders

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ABSTRACT

The term Autism spectrum disorder (ASD) refers to a neuro-developmental disorder that include repetitive behaviours, extremely constrained interests and deficits in social communication. In the last ten years, the numerous epidemiological papers discussing connection between autism and environmental chemical exposures has significantly increased. These findings are crucial because they focus on modifiable risk factors that may open up new possibilities for the primary prevention of the autism-related disability, which is now recognised to be more strongly related to environmental factors than was previously thought. A variety of environmental factors have been known as significant factors relevant to aetiology of ASD, such as lead and mercury (heavy metals), PCB(organic contaminant) and phthalates and BPA. The most accurate animal model of autism among all other models is valproic acid-induced autism, which can reproduce almost all of the molecular and cellular changes seen in humans with ASD. This review provide insight into various diagnostic available for autism, pathophysiology of autism and animal model of autism to develop a pharmacological therapeutic intervention for the treatment of disease..

Abbreviations:

ASD: Autism spectrum disorder
CDC: Centres for disease control and prevention
FMR1: Fragile X-Syndrome
ASD-OC: Autism spectrum disorder-observation for children
ASD-DA: Autism spectrum disorder-Diagnosis scale for intellectually disabled Adults
CNV: Copy number variation
VPA: Valproic acid
BPA: Bisphenol A
IL-6: Interleukin
TNF: Tumor necrosis factor
THIM: Thiomersal

1. Introduction

Autism spectrum disorder (ASD) is a neurological illness marked by social interaction deficit, limited interest and repeated behaviour (Hodges *et al.*, 2020). In the recent stats of centre for disease control (CDC) of united state (US), one in every fifty- four people has an ASD (Patrick *et al.*, 2021). Males have a 4-fold higher prevalence than females (de giambattista *et al.*, 2021). Indeed numerous children with ASD have medical comorbidities like sleep disturbances, (gastrointestinal) GI abnormalities, mitochondrial dysfunction, and epilepsy (Rossignol *et al.*, 2012). Fragile X syndrome (gene associated FMR1), tuberous sclerosis (gene associated TSC1 - TSC2) and Rett's syndrome (gene associated MECP2) are three potential genetic disorders associated with ASD (Freitag *et al.*, 2007). There are currently no diagnostic biomarkers available so ASD is diagnosed based on symptoms such as repetitive behaviours and impaired social communication and interaction. Several genetic and non-genetic risk factors either alone or in combination have been identified and are linked to the development of ASD but cause of ASD is still unknown. Several patho-mechanisms have been proposed to contribute to these behaviours including changes in brain development and function as well as synaptic defects (Sauer *et al.*, 2021).Although there is no cure prompt and adequate intervention can dramatically enhance one's quality of life. Aripiprazole and risperidone are two commonly prescribed atypical antipsychotic drugs that can help with ASD comorbidities till date. Thus, research is being done to manage diseases at the moment and animal testing is being done to develop the best drugs. There are various promising animal model that construct validity, face validity and predictive validity (Schroeder *et al.*, 2015).Despite progress in our understanding of anatomical and physiological variation in animal models for ASD and in the brains of autistic/non-autistic individuals of ASD, investigators have found it difficult to translate findings from murine species to humans owing to contradiction between the experimental approaches employed to assess for ASD phenotypes (Scott *et al.*, 2021). In this review various animal models are discussed which can help in finding a treatment for autism.

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2. Sign and Symptoms

Despite the fact that people with ASD are diverse the disease is defined by key traits in two areas that are restricted repetitive sensory motor behaviour and social communication regardless of ethnicity, culture and race. Symptoms included considerable impairment in nonverbal behaviours such as body postures, facial expression, eye gaze, recurrent stereotypical behavioural pattern, lack of interest in social activities, Atypical social behaviour, failure of normal back and forth discussion, lack of interest and emotion sharing. Patient with ASD usually has problem in maintaining and understanding relationships, issues in adapting behaviour to varied social circumstances, sharing imaginative play. However inspite of the above symptom patient also suffer from insistence on consistency, rigid adherence to ritualistic patterns of verbal and non-verbal behaviour, intense anxiety at little change, trouble with transformation or rigid thought process (Lord *et al.*, 2018).

3. Diagnosis

To improve the condition of ASD patients a reliable instrument and scale should be utilised to precisely assess the ASD patient status as the symptoms of ASD are complex and overlapping with other psychiatric disorders (Baird *et al.*, 2003). Assessment of disorder can be done by direct patient observation, parent and patients interview and detailed clinical assessments for ASD which include a thorough review of family history (Leekam *et al.*, 2002). There are some of the scales that are commonly used to diagnose ASD such as The Diagnostic, Developmental and Dimensional Interview (3di) involves participation of parents along with the patients in order to carry out investigation which relies on both computer based as well as investigator (Skuse *et al.*, 2004). The ASD-Observation for Children (ASD-OC) is a forty-five item observatory index used to observe and assess core autistic symptoms such as repetitive behaviours, social impairment and communication difficulty (Neal *et al.*, 2014). The ASD- Diagnostic index for Intellectually Disabled Adults (ASD-DA) is a diagnostic index enable to individualized the adults having ID (intellectual disability) only and adult who have ID with ASD (Matson *et al.*, 2008).

4. Pathogenesis

ASD pathogenesis is multidimensional and uncertain with factors such as unbalanced excitatory/inhibitory networks, calcium signalling, defective neural migration, abnormal dendritic morphology, mirror neuron theory, neuro-immune disturbances and disrupted neural connectivity (Watts *et al.*, 2008). Idiopathic ASD, which accounts for the majority of cases, has been identified as ASD caused by no known specific cause. Various environmental variables, namely maternal immune activation and prenatal exposed to chemicals have now been proposed to predispose to idiopathic ASD. Whereas De novo mutations have been identified as one of the known genetic causes of ASD in approximately 20-30per cent of cases (Varghese *et al.*, 2017). There are three types of genetic abnormalities associated with ASD: at least 5per cent are the result of alteration in single gene similar to those seen in MECP2, FMR1 and SHANK; copy number variations (CNVs) account for around ten percent of all mutations which include translocation, significant deletion, duplication or inversion in chromosome and as a result of the accumulation of common variations many are polygenic risk factors each of which contributes a percentage of the risk (Iossifov *et al.*, 2014).

5. Neuropathology

Global issues with brain development is observed in young autistic children in the cortex, cerebellum and other subcortical regions with severity of neuropathology varying by location (Varghese *et al.*, 2017). The inferior cortex (frontal) is important in forming connections between words to express and conclude concepts, imitation, language production and empathy. The significantly reduced size of pyramidal neurons in patients with ASD shows that communication across great distances may be hampered which is supported by comparable neuropathological findings in areas interacting with the inferior frontal cortex (Jacot *et al.*, 2012). Several studies have found that in the hippocampus of ASD patients neuron size is smaller cell packing density is higher and dendritic arborization is less complex indicating that neuronal development is impaired (Durak *et al.*, 2016). In the subependymal layer there is disorganisation of white and grey matter in the form of thickening (Heterotropia). Individuals with ASD may have a disordered cortex structure with misplaced neuronal clusters (Dysplasia). Dysplasia and Heterotropia may occur simultaneously in the same person. These problems in ASD patients are due to alterations in neuronal development and migratory processes (Wegiel *et al.*, 2010). In young autistic children aged 36-56 months there is a 13-16 percent abnormal enlargement of the amygdala. According to latest research enlargement of the amygdala is linked to increased anxiety, poor social and communication skills (Amaral *et al.*, 2008).

6. Animal Models of Autism

Despite the fact that ASDs are unique to humans, animal model can be utilised to gain insight into the fundamental biology and allow for the design and testing of therapeutic

agents. Because there are so many potential environmental elements that can cause autism a well-defined animal models should be capable of expressing basic symptoms of the disorder. The use of an ASD animal model induced by medications or other chemicals has the advantage of being simple, rapid and inexpensive. However each animal model just depicts a portion of the possible aetiology of ASD (Li *et al.*, 2021).

7. Valproic Acid (VPA) Induced Model

Prenatal exposure to VPA (anti-epileptic drug) causes ASD in humans and autistic like behaviour in rodents making it an excellent model for studying the neural basis of ASD. Both in humans and in mice exposed to VPA in utero a relative increase in excitatory and inhibitory synaptic function has been proposed as a pathogenetic mechanism of autism (Taleb *et al.*, 2021). By inhibiting the activity of histone-deacetylase (HDA) VPA modulates neurotransmission and regulates gene expression via epigenetic chromatin remodelling. VPA inhibits HDA directly causing transient hyperacetylation in the brain inhibiting transcription increasing apoptotic cells and decreasing cell proliferation in specific areas of the brain (Nicolini *et al.*, 2018). VPA exposed rat shows decreased dendritic spine density in the prefrontal cortex but an elevation in ventral hippocampus spine number.

Offspring of VPA-exposed rats show alterations in serotonin levels in the brain (prefrontal cortex, hippocampal area and cerebellum) that are similar to the findings of current human clinical investigations implying that VPA application could be a promising choice for developing animal models of ASD (Li *et al.*, 2021).In contrast to the general population where males are 4-times more prone than females to acquire autism the maternal VPA challenge appears to harm both female and male rodents. In children exposed to VPA during pregnancy a 1:1 male to female ratio has been commonly observed indicating that valproate may pose a higher risk for females. The molecular changes seen in people with idiopathic autism are similar but not identical to those seen in the VPA model (Mabunga *et al.*, 2015).

Sodium salt of valproic acid (NaVPA, Sigma) was dissolved in 0.9% saline for a concentration of 150 mg/ml (pH 7.3). The dosing volume was 3.3 ml/kg; the dosage was adjusted according to the body weight of the dam on the day of injection. Single ip injection of 500 mg/kg NaVPA was given to dams to induce autism (Markram *et al.*, 2008).

8. Bisphenol A (BPA) Induced Animal Model

BPA is an endocrine disrupting chemical found in everyday products such as canned food linings, thermal receipts and plastic water bottles. In utero BPA exposure reduce neuronal viability and density in the hippocampal area and impede learning & memory only in male offspring while females were unaffected (Thongkorn *et al.*, 2019). The molecular biology behind the neurological effects of BPA exposure are immensly complex. They include changes in neuro-endocrine function of hormonal axes, neurotransmitters, mitochondria, neuropeptides, inflammatory effects and calcium imbalances (Mustieles *et al.*, 2015). Prenatal BPA exposure changes neuronal functions such as neurogenesis in the hippocampal area and synaptic density in mouse models according to recent studies (Kim *et al.*, 2009). BPA has been shown in animal studies to be an endocrine disruptor mimicking the effects of the hormone oestrogen. BPA has been linked to effect similar to estrogen in rodents such as alteration in foetal & neonatal prostrate glands as well as breast tissue (Rebolledo *et al.*, 2021).

BPA (5 mg/kg) was administered intraperitoneally to Wistar albino mothers throughout their pregnancies and up to the third postnatal day (PND) to induce autism. After that the Pups underwent behavioural testing on the 21st PND (Singha *et al.*, 2022)

9. Propionic Acid (PPA) Induced Animal Model

PPA is a preservative found in some foods such as wheat and dairy products and eating it can exacerbate ASD symptoms. Intra-peritoneal exposure of PPA to rat exhibited elevated levels of neurotoxic cytokines (interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), neurobehavioral abnormality (impaired social interactions) and microglia (CD68 positive) (Shultz *et al.*, 2014). PPA shows cellular and molecular mechanism by altering immune function, cell signalling, neurotransmitter production and secretion, functioning of mitochondria, lipogenesis, gating of gap junction, intracellular pH and expression of gene. In the development of autism like behaviour IL-6 plays a crucial role. Over expression of IL-6 resulted in neural circuit abnormalities, impaired cognition, altered anxiety related behaviour and reduced social interactions (Fabe *et al.*, 2011). Activation of apoptosis via increased pro-inflammatory cytokines have been linked to cell death of neuron. In the hippocampus of rats treated with PPA immuno-histochemical investigation showed reactive astrogliosis (GFAP), activated microglia (CD-68), but no apoptotic cell loss (Caspase -3 and Neu-N) (Choi *et al.*, 2018). Tiwari and coworker has investigated that the rats administered with PPA shows the decreased the levels of dopamine, acetylcholine and serotonin while the raised level of glutamate depicting the toxicity to neuron. The level of these neurotransmitter is restored by administration of PPA.

In order to induce Autism Wistar rats was exposed to multiple doses of PPA through ICV injection for 11 days. Upon ICV injection of PPA (4 µl/0.26 M) rats exhibit features similar to autism like behavioral and biochemical changes (Sharma *et al.*, 2019).

10. Thiomersal (THIM) Induced Animal Model

THIM (mercury-based preservative) found in a wide range of biological and pharmaceutical products (vaccine). THIM causes neurotoxic changes, death of neuron and causes apoptosis inducing factors to be released from mitochondria into the cytosol (Hornig *et al.*, 2004). THIM modifies the expression of apoptosis related factors. Several studies have revealed that increased oxidative stress, lipid peroxidation, decreased GSH level as well as mitochondrial dysfunction have all been linked to autism and mercury toxicity in the brain. In both Hg intoxication and autism loss of granule and Purkinje neurons in the brain (cerebellum) is a common finding. Hippocampal cell death, neurogenesis reductions, and severe learning difficulty are all caused by acute methyl-Hg exposure during development.Two week after one shot of Me-Hg in seven day old rat hippocampal size (21%) and cell number were reduced particularly in the granular layer of cell as well as in the hilus of dentate gyrus. (Hurley *et al.*, 2010). Neonatal THIM exposure can result in growth retardation and abnormal social interactions similar to those seen in ASDs (Abdelzaher *et al.*, 2021).

Thimerosal administered to rats at different doses (30, 300 or 3000 µg Hg/kg) in 4 intramuscular injections on 7, 9, 11, 15 PND. After birth on 5 and 8 day, behavioral test were performed on rat, to detect the locomotion activity, social interactions and stereotyped repetitive behaviors respectively. Data showed that Thimerosal at these doses (30, 300 and 3000 µg Hg/kg) impacted locomotory activity but at the dose 30 µg Hg/kg doesn't impaired social and stereotyped behaviors (Namvarpour *et al.*, 2018).

11. Future Perspective

Nowadays, VPA animal model of ASD is one of the most commonly used animal model. This model exhibit many similar structural and behavioral features that has been noticed in autistic individual. These similarities enable the model to define relevant pathways of developmental dysregulation resulting from environmental manipulation (Mabunga *et al.*, 2015). It is hoped that further improvement of these rodent behaviour evaluation will escalate their clinical finding translatability to healthy human phenotypes by using various techniques for example EEG (electroencephalogram), MR (magnetic resonance imaging) as well as development of novel preclinical socio-behavioural test and analytical methodology.

Conclusion

It is essential to determine the most appropriate animal model for effective use of animals in brain research. Because autism is a multifaceted disease all animal models such as VPA, BPA, PPA, and THIM may only be viewed as simulating one component of the aetiology of autism which is known as a reductionist view. Truely not all cases of ASD may be linked to VPA, BPA, PPA or THIM exposure nonetheless this alleged exposure may share the same etiological pathway as other etiological factors that contribute to the disease's development. The model can also make use of today's advanced technologies and techniques to precisely outline mechanistic pathways. In order to represent real-life scenarios involving the interplay between chronic exposure to a variety of chemicals and people's genetic origins, new integrative models that include biomonitoring, epidemiological, experimental, and computational approaches are still yet to be explored

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