Clinical Therapeutic Strategies to Ameliorate the Mitochondrial ETC Complexes Dysfunctions in Autism: First Time from India

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Abstract

Autism is a prototypical form of pervasive developmental disorder (PDD), characterized by complex behavioural impairments detectable as early as 18-36 months of age with severe abnormalities in communications, social awareness and skills, and the presence of restrictive and stereotyped patterns of behaviors, interests, and activities. In addition to these core symptoms, there are few other behavior disturbances which are commonly seen in the autistic individuals, such as anxiety, depression, sleeping and eating disturbances, attention issues, temper tantrums, motor disabilities and aggression or self-injury. Propionic acid (PPA) on oral and intraventricular injection of PPA in rodents mimics the behavioural and biochemical abnormalities observed in autism patients. Increased PPA levels may interfere with overall cellular metabolism in tricarboxylic acid cycle where it interferes with the conversion of succinyl co-A to succinate for generation of $FADH_2$ in electron transport chain complex II further impairs the ATP synthesis. Extracellular signals regulate various intracellular neuroprotective functions through secondary messenger's cyclic AMP (cAMP) that subsequently activate target enzymes Protein kinase A (PKA) & activate cyclic AMP responsive element binding protein (CREB) which regulate and protects various toxic damage in brain. Forskolin (FSK) (also called Coleonol) Coleus forskohlii Briq. (Lamiaceae), major pharmacological mechanism of action is linked to its direct action on adenyl cyclase (AC) enzyme which results in the increase intracellular cAMP/PKA/CREB pathway further responsible for various neuroprotective mechanisms. It is first time designed to investigate the protective and therapeutic potency of FSK in AC/cAMP/PKA mediated CREB activation in intraventricular PPA induced autism in rats.

Keywords: Autism; Propionic acid; Mitochondria; Forskolin; Oxidative stress

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Abbrivations: PDD: Pervasive Developmental Disorders; GSH-Px: Glutathione Peroxidase; PPA: Propionic Acid; CREB: cyclic AMP responsive element binding protein; MDA: Malondialdehyde; SOD: Superoxide Dismutase; BDNF: Brain-Derived Neurotrophic Factor and PDD-NOS: Pervasive Developmental Disorder Not Otherwise Specified.

Introduction

Autism is a severe and pervasive heterogeneous behaviorally neurodevelopment disorder, classified under the pervasive developmental disorders (PDDs). PDDs include Autism, Asperger's syndrome, Disintegrative disorder of childhood, Rett's syndrome [1,2]. It is characterized by impaired social interaction and communication, repetitive behavioral patterns, and restricted interests, hyperactivity, sensory disturbances, and sometimes self injury are also observed [3-5]. Clinical signs are usually present at the age of 3 years, but prospective studies of infants at risk have demonstrated that deficits in social responsiveness, communication, and play could be present early, at the age of 6–12 months [6]. Boys are three to four times more likely to have autism than girls with an overall incidence of 5/10,000 [7].

Pathological hallmarks of autism associated with mitochondrial dysfunction, oxidative stress, neuro-inflamamtion, neuro-excitation, abnormal synapse formation, over expression of glial cells in specific brain regions like cerebellum, cerebral cortex, amygdala and hippocampus [8-11]. In Autism patients, abnormalities in neurotransmitter systems like frequently decrease in gamma amino butyric acid, increase in glutamate leads to excitotoxicity, hyper level of dopamine and dysregulation of serotonergic system & oxytocin in several brain areas like cerebellum, parietal cortex, superior frontal cortex, hippocampus, amygdala have been reported [12,13]. There are several lines of evidence in previous studies which have demonstrated that patients with autism show the alterations in malondialdehyde (MDA), a lipid peroxidation product, together with decreased levels of main scavenger enzymes, such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), heat shock protein 70 (Hsp70), in serum [14]. Individuals with autism may show enlarged brain size in the first few years of life, with altered migration of cortical, amygdala and cranial nerve motor neurons, as well as cerebellar neurons [15]. Patients with autism are often reported to suffer from a variety of bowel dysfunctions and gastrointestinal disturbances [16].

There has been a growing interest in the literature on possible environmental agents involved in the development of autism, such as chemical toxins, which could act during critical periods of pre- and early postnatal development [17]. For example there is increased risk of autism in children exposed prenatally to thalidomide, valproic acid, and ethanol, propionic acid [18]. A sedative or anti-vomiting medication (Thalidomide), during pregnancy which was not only associated with limb deformities but also an Autism-like behavioral disorder in the offspring [19]. Anticonvulsant valproic acid (VPA) indicates that not only has VPA teratogenic effects but also rats exposed to VPA during gestation show deficiencies similar to those of autism [20]. Propionic acid (PPA) is an intermediary in cellular fatty acid metabolism, it is a short chain fatty acid and found in high levels in the gut, along with a number of other short chain fatty acids, such as acetate and butyrate & all of these are a major metabolic end product of enteric bacteria [21]. The Clostridial, Desulfovibrio & Bacteriodetes species are PPA producing enteric bacterial species, have been isolated from patients with regressive autism [22]. PPA is commonly used as a food preservative in the dairy products, added to refined wheat and is also present naturally in a variety of foodstuffs [23,24]. Propionic acid (PPA) is a weak organic acid that can cross the lipid bilayer of neuronal membranes and cause mild, reversible intracellular acidification, which can produce wide spread effects on neurotransmitter release involving glutamate, dopamine, and serotonin, each of which can influence locomotion and other behaviors [24-27]. PPA through oxidative mechanisms inhibits Na+/K+ ATPase and increases glutamate receptor sensitivity which can enhance neural depolarization leading to neural hyper excitability in brain regions linked to locomotors activity [28,29]. It also promotes intracellular calcium release, excessive levels of Ca2+ in the mitochondria can affect the mitochondrial metabolism, increase the oxidative stress and plays a key role in synaptic transmission in the brains of individuals with autism [30]. Increased PPA levels may interfere with overall cellular metabolism in tricarboxylic acid cycle where it interferes with the conversion of succinyl co-A to succinate for generation of $FADH_2$which was consumed by the complex-II and further impairs the ATP synthesis leads to mitochondrial dysfunction and -interfere with overall cellular metabolism [31]. A number of studies recently have reported that over 30-50 percent of children with autism have biomarkers of abnormal mitochondrial function suggesting that a relatively high percentage of individuals with autism might have some degree of mitochondrial dysfunction. Mitochondrial dysfunction has been demonstrated to be associated with neuropsychiatric conditions [32]. In case of autism

abnormal mitochondrial function in the dorsal prefrontal cortex was measured that significantly correlated with the severity of language and neuropsychological deficits in the autism [33]. Some of the symptoms of mitochondrial dysfunction, such as neurological disabilities, mental retardation, learning disabilities, seizures and gastrointestinal disturbances, are also present in a subset of individuals with autism [34]. The mitochondrial dysfunction was also occurs in cerebellum, temporal lobe, anterior cingulate cortex and thalamus [35].

cAMP is recognized as universal cell regulator function. cAMP is produced from its precursor, ATP, through the catalytic activity of the ACs [36]. The balance of cAMP signaling is essential to multiple cellular processes, including immune function, growth, differentiation, gene expression and metabolism [37]. A member of neurotrophin family, BDNF (brain-derived necrosis factor), initially identified as a survival factor for peripheral neurons, has emerged as a critical factor that regulates synaptic development and plasticity in the central nervous system [38], where cAMP seems to be important for signaling & biological function of BDNF. Moreover, the survival of retinal ganglion cells by brain-derived neurotrophic factor (BDNF) is dependent on cAMP [39]. cAMP can activate the cAMP dependent protein kinase (cAK or PK_A), which in turn phosphorylates the cAMP responsive element binding protein (CREB) [40]. cAMP dependent PK_A mediated activation of CREB which is a constitutively expressed transcriptive agent in the nuclei from hippocampal neurons, in the inner mitochondrial compartment as well as in the nucleus [41]. Elevation of cAMP causes both short and long-term increase in synaptic strength [42]. CREB was play a critical role in the neuronal survival and function including formation and retention of memory [43]. cAMP/PK_A/CREB activation has too been reported to induce long term memory (LTP) potentiation and inhibit apoptotic and necrotic cell death [44,45]. Conversely, preclinical and clinical findings now suggest that impaired CREB phosphorylation may be a pathological component in neurodegenerative disorders [46].

Forskolin a major diterpenoid isolated from the roots of *Coleus forskohlii*, directly activates the enzyme adenylcyclase thereby increasing the intracellular level of cAMP and leading to various physiological effects. There are several researches for neuroprotection but treatment options for autism are still limited to supportive care and the management of complications. At present many drugs are available but they provide only symptomatic relief, not stop progression of this typical disease. Thus, the development of new therapeutic strategies remains an unmet medical need. Failure of current drug therapy may be due to their action at only one of many neurotransmitters involved or their inability to up regulate signaling messengers reported to have important role in neuronal functioning, neurotransmitter biosynthesis and release neuronal growth and differentiation, synaptic plasticity and cognitive functioning. Mitochondrial dysfunction was occurs mostly in the autistic individuals, due to which there is decreased level of cAMP responsible for low production of ATP. Therefore, as already mentioned above, one of the alternatives to enhance the levels of cAMP secondary messengers or to enhance CREB phosphorylation can be achieved directly through a specific phytochemical Forskolin (FSK) obtained from *Coleus Forskohlii* which activates these cyclic nucleotides and further performed extensive neuroprotective functions in autism related disorders.

Based on important and versatile role of cAMP/PKA/CREB signaling in regulation of neuronal functioning, the present study was designed to investigate the role of cAMP mediated CREB activation in propionic acid (PPA) induced experimental Autism disease in rats and to find out if cAMP mediated CREB pathway is equally implicated in the disease pathogenesis or progression. Further the studies were extended to understand the disease pathogenesis and to investigate and discuss the various possible central mechanisms involved in the effect of such targets using behavioral paradigms and biochemical markers of neurodegeneration.

Autism

Autism is the prototypical form of pervasive neuro developmental disorders (PDDs), characterized by complex behavioural impairments detectable as early as 18–36 months of age. The slippages or shortfalls are frequently exhibits in province such as social interaction, communication, and are also associated with stereotypic, repetitive and restrictive behaviour and interests [1]. The disorder is commonly go along with sensory processing abnormalities, sleep problems, anxiety and depression , hyperactivity, aggression & self-injurious behaviours , seizures and eating or digestive problems, surrounded by others [47]. Autistic disorder was classified in the category of 'pervasive developmental disorders', which included 4 other disorders: (a) Asperger's syndrome, which was distinguished from autism by the absence of language and cognitive delay, (b) disintegrative disorder of childhood, characterized by a period of normal development of 2–4 years followed by the onset of autistic

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symptoms, (c) Rett's syndrome, the genetic etiology of which is known and which affects only Girls, (d) pervasive developmental disorder not otherwise specified (PDD-NOS) [48]. The conceptualization of these disorders has changed dramatically over the past 10 years, which is reflected in the DSM-5, the new edition of the DSM manual published in May 2013, which leading to the collapse of the earlier diagnostic categories of pervasive developmental disorders into a single category of autism spectrum disorder or ASD [49]. It is not surprising that the etiology of autism is thought to be similarly heterogeneous and multifaceted in nature. The broad spectrum in the definition of autism suggests that the disease may result from exposure to certain environmental agents instead of primarily a genetic disorder [50]. Imaging and neuropathological studies of autism patients have noted increased brain size, white matter abnormalities as well as increased neuronal density in neocortical, limbic and cerebellar areas [51]. Post-mortem studies have shown a reduction in neuron number in the amygdala, fusiform gyrus, and cerebellum, and signs of persistent neuroinflammation and also show the alterations in corpus collasum, hippocampus grey matter & white matter. In autism, altered immune processes affect a wide array of neuro developmental processes (eg, neurogenesis, proliferation, apoptosis, synaptogenesis, and synaptic pruning), with persistent active neuroinflammation, increased concentrations of pro-inflammatory cytokines in serum and cerebrospinal fluid, and altered cellular immune functions [52]. In autism, alterations in both serotonin and γ-aminobutyric-acid (GABA) systems have been reported quite consistently, such as hyperserotonaemia and an altered developmental trajectory of brain serotonin synthesis capacity, and reduction in the expression of GABA synthetic enzymes and receptors [53,54].

History of Autism

A biological origin for autism was proposed even in the first scientific account of autism, which was followed by the first neurobiological account that dispelled some myths about autism [55]. Researchers observed similar behaviours in autism and in frontal lobe damaged patients. They found an impaired dentato-thalamocortical pathway, which plays a critical role in language and higher cognitive functions in autism. A decade later, using positron emission tomography (PET), found a global increase in resting glucose metabolism in adults with autism, which provided indirect support for autism being linked to abnormal brain activity .Furthermore, genetic studies starting from the 1980s have also helped

emphasize the biological origin of autism by providing strong evidence of heritability [56].

Prevalence

Over the last 3 decades, a substantial increase in the prevalence of autism has been reported, from 4 to 5 per 100,000 in the 1960s to around one in 45 children today. In the past decades, the prevalence of autism has shown rapid growth. The first prevalence estimate of autism, was 4.5 per 10,000 (about one out of 2222) children aged 8 to 10 in the southeast of England [57,55]. Autism was once thought to be relatively rare, but recent population-based studies in developed countries have reported a rise in prevalence estimates when the broader definition of autism (i.e. Autism Spectrum Disorder) is used to ascertain cases. The most recent reported highest prevalence estimate of autism in the US was 200 per 10,000 (about one out of 50 people), in UK was 157 per 10,000 (about one out of 64 people), and in Asia was 264 per 10,000 (about one out of 38 people) an increase in prevalence has also been found in Sweden [58,59]. Hence, the increasing prevalence of autism appears to be a worldwide phenomenon. The prevalence of autism in children with epilepsy is higher than in the general population; with an estimated frequency varying from 5% to 32%.Previous studies consistently report a sex difference in the prevalence of autism of 4.5:1 males to females. Males with autism are more likely to exhibit repetitive and stereotyped behaviors, whereas females with autism have higher rates of severe cognitive and developmental delays [55]. Prevalence of autism has been reported to be two times higher in cities where many jobs are in the information-technology sector than elsewhere; parents of children with autism might be more likely to be technically talented than are other parents.

Symptoms of Autism

Autism is associated with abnormalities in various brain regions such as the neocortex, hippocampus, amygdala, and basal ganglia, which mediate social interaction, communication and repetitive behaviors. From the original description of autism, repetitive behavior has been a defining feature of autistic disorder [60]. A wide range of specific forms of abnormal repetition has been identified in association with autism including stereotypy, rituals, compulsions, obsessions, insistence on sameness, echolalia, self-injury, tics, dyskinesia, akathesia, and perseveration. Such behaviors can be observed across individuals with autism, and multiple categories of abnormal repetition can occur within the individual with autism [61,62].

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Motor Symptoms: A growing body of research supports the presence of diverse motor impairments in persons with autism including motor anticipation, clumsiness, impaired postural control, dyspraxia, and impaired gross and fine motor movements. The motor deficits tend to be debilitating, since they can interfere with daily activities and academic achievement.

Dyspraxia: The various forms of dyspraxia can exist together or separately in autism. Praxis is the ability to conceptualize, plan, and successfully complete motor actions in novel situations [63]. Developmental dyspraxia, that is, failure to have acquired the ability to perform appropriate complex motor action. Developmental dyspraxia is categorized around problems related to transitive gestures (pantomimed tool use), intransitive actions (symbolic gestures such as waving goodbye), imitative actions (such as imitating meaningless hand or body postures), motor planning, and difficulty conceptualizing novel ways to interact with objects [64,65].

Gait and Gross Movements: Within a decade, however, there was growing recognition that individuals with autism experience motor difficulties. Unusual gait, including slower pace, decreased step length, increased knee flexion, and unusual upper extremity positions during walking, were described in individuals with autism. Gross motor development (supine, prone, rolling, sitting, crawling and walking) and movement abnormalities were examined in the home videos of infants later diagnosed with autism [66,67].

Non-Motor Symptoms
Repetitive behaviors: Repetitive behaviors appear in many other neuro developmental and neuropsychiatric disorders. Repetitive behavior refers to a broad class of responses characterized by their repetition, rigidity or inflexibility, and frequent lack of obvious function. Repetitive behaviors described in individuals with autism include stereotyped motor movements, repetitive manipulation of objects, repetitive self-injurious behavior, specific object attachments, compulsions, rituals and routines, an insistence on sameness, repetitive use of language, and narrow and circumscribed interests [68,61].

Anxiety: Anxiety is a real difficult for many adults with autism or Asperger syndrome. It can affect a person psychologically and physically. Anxiety, a behavioral symptom of autism, is characterized by psychological symptoms like easily losing patience, difficulty concentrating, difficulty sleeping, depression and thinking constantly about the worst outcome. The physical symptoms include excessive thirst, stomach upsets, loose bowel movements, frequent urinating (going to the loo), periods of intensely pounding heart, periods of having gas, muscle aches, headaches, dizziness, pins and needles and tremors.

Cognitive dysfunctions: Cognition refers to the mental processes involved in perceiving, attending to, remembering, thinking about, and making sense. Autism are thought to have a specific profile of cognitive strengths and weaknesses - difficulties appreciating others' thoughts and feelings, problems regulating and controlling their behavior, and an enhanced ability to perceive details [69].

Genetics in Autism
The heritability of a phenotype gives an indication of the extent to which it is controlled by genetic factors and can be calculated from concordance rates. Thus, the heritability of ASDs has been estimated to be 90%, making ASDs the most heritable of the childhood onset neuropsychiatric disorders. Syndromic autism, with a single gene etiology and co-occurring with other physical features in addition to autism, accounts for approximately 10% of cases [70,71]. Non-syndromic ASDs represent the larger percentage of cases. The proposed genetic alterations are copy number variants (CNV's), which cause gene dosage effects, and common genetic variation, such as single nucleotide polymorphisms (SNP's). It has demonstrated that there is a direct correlation between the autism phenotype and the number of CNVs, with the number of CNVs in the parents of autistic children being intermediate between the pro bands and the controls. Hence, an increase in the number of CNVs increases the probability of developing autism. The copy-number variants (CNVs)—that are small gain or loss of genomic DNA—are robustly detected. De novo CNVs are present in 4–7% of the patients with ASD compared with 1–2% in unaffected siblings and controls [72]. The most common CNV occurred at 15q11–q13.3. This region encompasses the UBE3A gene, deficiency of which we have shown in a mouse mutant specifically alters the hippocampal mitochondrial morphology and brain complex II/III specific activity. It is also found increase in the percentage of de novo CNVs in families with one affected child and implicated post-synaptic density genes such as SHANK3, NLGN4 and NRXN1, as well as other genes encoding proteins in the synaptic complex, such as DPP10 [73]. Several factors support a role for the dopamine b-hydroxylase (DBH) gene, which has been mapped to 9q34, in the etiology of autism. The DBH gene encodes a protein that catalyzes the conversion of dopamine to

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norepinephrine [74]. The activity of the mitochondrial inner membrane calcium regulated aspartate/glutamate carrier (AGC) gene, SLC25A12, and/or its expression have also been reported to be increased in autistic patients, at least in part due to elevated levels of calcium in the brains of autism patients [75,76]. Glutamic acid decarboxylase 1 (GAD1) gene and the distal-less homeo box (DLX) genes are attractive candidates based on their biological functions. These combinations of functional mutations in GAD1 and DLX genes may alter the inhibition/excitation ratio in some parts of the brain [77]. Human genetic studies have found a link between a short variant of the serotonin transporter allele (SERT) and autism [73]. Mice with targeted disruption of the *Sert* locus evidence marked decreases in brain serotonin levels, as well as decreased aggression, increased anxiety, and increased depression-related responses, including longer immobility in a forced swim task. The regulation of gene expression may be of importance in ASDs in keeping with GWAS and candidate gene studies [78].

Neurochemistry of Autism

Serotonin in Autism: Serotonin, as a monoamine neurotransmitter and hormone, plays numerous roles and is a critical modulator of neuronal interaction that supports diverse behaviors and physiological processes, and acts via different specific transporters, receptors, and intracellular signaling pathways. Multiple lines of evidence implicate abnormal serotonergic signaling in psychiatric and neuro-developmental pathogenesis [79]. Serotonin reduces neural activation of inferior frontal and striatal inhibitory control regions and increases activation of cerebellum, temporal and parietal lobes. In autism decreased activation in right inferior frontal and increased activation in left inferior frontal cortices observed [80,81]. In autism abnormal activation in classical inhibition areas [82] of inferior frontal cortex, basal ganglia, thalamus and cerebellum; in frontal cortex, caudate and thalamus this was correlated to the severity of restricted, stereotypical and repetitive behavior. Individuals with autism have abnormalities in the serotonergic system including physiology, neurobiology and genetics [83]. Deregulation of the developing serotonergic system could occur by various mechanisms, including mutations in genes encoding transcription factors involved in specification and patterning of 5-HT receptors or neurons [84].

The disruption of the serotonergic system is one of the most consistent observations associated with autism [85]. Brains of individuals with ASD display significantly lower concentrations of serotonin compared with the brains of non autistic individuals [86]. A developmental peak in serotonin synthesis occurs in the brain before puberty and is thought to play a role in growth and differentiation of neurons during brain development. This peak fails to occur in children with autism [87]. Several studies have reported that approximately 1/3rd of all autistic individuals have elevated levels of whole blood (or platelet) serotonin [88]. Hyperserotonemia, which is believed to be caused by abnormal maturation of the serotonin system, is also suggested to be either directly or indirectly responsible for the immune abnormalities observed among autistic subjects [89,90]. The high serotonin concentrations in peripheral blood cells from individuals with autism have been suggested to be the result of increased serotonin synthesis in the gut; however, the cause of the elevated serotonin production in the gut [91]. In individuals with autism, further decreasing their brain serotonin by acute depletion of tryptophan exacerbates symptoms such as repetitive behaviors and facial recognition patterns revealing a continuing requirement for serotonin in modulating these behaviors. These data suggest that disruption in serotonin levels are linked to autism, although no underlying mechanism has been identified [92,93].

Oxytocin in Autism: Oxytocin (OT) is a nanopeptide produced in the magnocellular neurosecretory cells in the supraoptic nucleus and the paraventricular nucleus (PVN) of the hypothalamus. It is released into the blood from the posterior lobe of the hypophysis, as well as directly from the perikarya, dendrites or axon collaterals of magnocellular neurons. OT fibers have endings in a variety of different brain areas, including the thalamus, the hippocampus, the amygdala, the pineal gland and the cerebellum [94]. In humans, OT regulates social interactions, social cognition, social behavior and fear [95-97]. Rodents with abnormal OT have been proposed as potential animal models for autism [98,99]. Studies done in autistic children have shown decreased plasmatic OT [100]. More recently it has been reported that mean plasma oxytocin levels do not differ between autism and comparison groups; rather, levels were observed to be positively associated with social functioning across groups [101].

Melatonin in Autism: Sleep problems in autism might occur as a result of complex interactions between genetic and social/environmental factors [102]. Proposed hypotheses of sleep dysregulation in autism include abnormalities in the hypothalamic–pituitary–adrenal axis regulating circadian rhythms and alteration in hormone/neurotransmitter (melatonin/serotonin) production [103]. It was hypothesized that abnormalities

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in melatonin secretion may play a role in the development of autism [104]. The biosynthesis and molecular action of melatonin (5-methoxy-*N*-acetyltryptamine) have been thoroughly studied. Melatonin is mainly synthesized by the pinealocytes in the pineal gland [105]. Sleep problems in children with autism spectrum disorders are common, with a prevalence of 44–83% [106] and contribute to significant morbidity in children and to familial stress. It is produced by the conversion of serotonin to N-acetylserotonin (NAS) by the rate-limiting enzyme AA-NAT (arylalkylamine N-acetyltransferase), followed by the conversion of N-acetylserotonin to melatonin by ASMT (acetylserotonin methyltransferase), and also known as HIOMT (hydroxyindole O-methyltransferase) [107]. Levels of acetylserotonin methyltransferase, an enzyme necessary for the production of melatonin, have been found to be significantly lower in individuals with autism compared with control subjects [108]. NAS is intermediate metabolite it is an agonist of the TrkB receptor and may therefore share the neurotrophic properties of brain-derived neurotrophic factor, the canonical TrkB ligand [109,110]. The intermediate NAS might also be altered, which causes the alterations of the serotonin-NAS–melatonin pathway which might constitute a possible biomarker for a subgroup of individuals with autism [111].

Figure 1: Chemical Structure of the Melatonin.
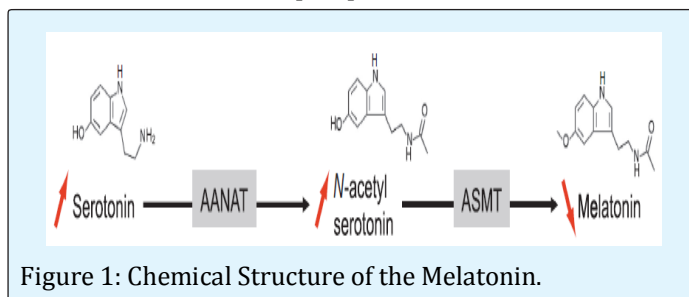
At a metabolic level, NAS is an inhibitor of tetrahydrobiopterin synthesis, a cofactor of several pathways such as nitric oxide formation and tyrosine/bioamine synthesis. Thus, in addition to the possible consequences of alterations of serotonin and melatonin, NAS accumulation may have implications for the pathophysiology of autism [112-114]. ASMT is also an excellent candidate for susceptibility to ASD because it encodes the last enzyme in the melatonin biosynthesis pathway [115]. Melatonin has been reported to have many actions in humans, including effects on sleep, regulation of circadian rhythm, oxidation of free radicals, augmentation of immune responses, and inhibition of reproductive processes, as well as antiaging properties [116,117]. Autistic disorder is signalized by communication and social interaction impairments

associated with repetitive interests and behaviors, improvement of communication, social withdrawal, stereotyped behaviors and rigidity or anxiety was reported in children with autism using melatonin [118-121]. Although melatonin is best known for its role as a key regulator of the circadian rhythm, it is also a potent antioxidant, has anti-inflammatory properties, is involved in the immune response, and helps regulate synaptic plasticity [105]. It have shown that blood melatonin and nocturnal excretion of 6-sulphatoxymelatonin (6-SM), the predominant metabolite of melatonin, are reduced in children with autism [122], due to genetic abnormalities influencing the enzyme necessary for the production of melatonin.

Dopamine in Autism: Dopamine (DA) is a catecholamine that is synthesized from the dietary amino acid tyrosine. Once ingested, tyrosine is hydroxylated (by tyrosine hydroxylase) into L-dihydroxyphenylalanine (L-DOPA). This is the rate-limiting step of the synthesis of dopamine. L-DOPA is then converted to dopamine via the enzyme DOPA decarboxylase [123]. In general, the dopaminergic system is thought to affect a wide range of behaviors and functions, including cognition, motor function, brain-stimulation reward mechanisms, eating and drinking behaviors, sexual behavior, neuroendocrine regulation, and selective attention [124]. Dysfunction in dopaminergic signaling may be an underlying cause of autism [125]. The dopamine (DA) transporter (DAT) plays a critical role in regulating the strength of dopaminergic tone by clearing extracellular DA [126]. The neurobiology of repetitive and stereotyped behaviors is only partially understood but the basal ganglia—frontal lobe circuitry plays an important role [127]. Part of this circuitry is regulated by the dopamine system, which may explain the high prevalence of motor rigidity and cognitive rigidity in ASD. It has been reported that dopamine is increased in frontal cortex (FC) [128]. Hyper activation of the DA system in people with autism has been suggested by several clinical reports [129]. Maternal stress and its resulting increase in corticosteroid levels elevates DA activity and is a major risk factor for numerous neuro developmental disorders, including autism [130,131]. Three sets of findings comprise the main evidence that over-activation of DA systems represents the most characteristic brain dysfunction in autism. They are: (1) the link between hyperdopaminergic activity and the various behaviors characteristic of at least high-functioning autism; (2) the relation between autistic deficits and right-hemispheric dysfunction; and (3) pharmacological evidence, including assays of DA activity and efficacy of anti-DA treatments [132]. An autistic patient is a characterized by

impairments in communication and social interaction as well as patterns of restrictive, repetitive interests and behaviors during early childhood. All of these disturbances can be traced, in varying degrees, to DA over-activation. Use of medications during pregnancy was identified byas being one of the prenatal factors most frequently related with autism. DA is highly vulnerable to a variety of direct and indirect prenatal influences, and the prenatal-DA link in autism is precisely accentuate by the finding that mothers of autistic children are twice as likely to have two missing alleles for the dopamine-beta-hydroxylase (DBH) enzyme, thereby dominant to chronically high maternal DA levels because of the failure to follower DA to NE by means of the DBH enzyme [133,134].

Glutamate in Autism

Glutamate is the most prominent excitatory neurotransmitter. Glutamate modulates synaptic plasticity, vital to memory, learning and regulation, and modulates gene expression. Overstimulation of glutamate receptors leads to excitotoxicity, creating oxidative stress, mitochondrial damage and ultimately may play a role in neurodegeneration [135]. Glutamate receptors are divided into metabotropic and ionotropic receptors are further classified into the following three families: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and Kainate. Several researchers have postulated that glutamate dysfunction may play a role in autism [136]. It was suggested that hyperglutamatergia in the brain is involved in the pathophysiology of autism. Levels of GAD 65 kDa and GAD 67 kDa proteins, both of which are involved in converting glutamate to GABA, are reduced in the brains of individuals with autism, resulting in increased levels of glutamate in the brain substrate [137]. According to previous studies, in autism the involvement of glutamate levels in four brain regions which are bilateral anterior cingulate, left striatum, left cerebral hemisphere, and left frontal lobe. As cerebellum is involved in several processes that include cognitive, affective and sensory functions in addition to motor tasks. Attention related cerebellar function is usually reduced in autistic individuals [138]. Another study relates anterior cingulate dysfunction to deficits in joint attention and social orienting in autism [139], and different parts of the striatum may participate in different types of memories [140]. In addition, the frontal lobe is central to many functions that are associated with autism, such as language and executive functions such as working memory, inhibition, planning, organizing, set-shifting, and cognitive flexibility [141]. An excess of extra neuronal glutamate can interfere with neuronal migration patterns,

differentiation and synaptic development, resulting in varying degrees of abnormal brain architecture and hence differing severities of autistic features [142]. The increased probability of epilepsy in patients with autism suggests enhanced glutamatergic signaling with positive correlation between plasma levels of glutamate and the severity of autism and increased expression of mRNAs encoding the AMPA 1 receptor in the cerebellum of autistic patients [143,144]. The mRNA levels of genes, including excitatory amino acid transporter 1 (EAAT 1) and AMPA-type glutamate receptor, are significantly increased in the brain of autism, suggesting abnormalities of glutamatergic neurotransmission in the pathogenesis of this disorder [145]. Activation of ionotropic glutamate receptor, AMPA, kainite and NMDA opens ion channels for sodium ions and Ca2+. Overstimulation of NMDA receptors is one of the mechanisms for Ca2+ overload in neurons and glutamate neurotoxicity [146,147]. Excessive activation of the NMDA receptors increase intracellular Ca^{2++} concentrations, triggering a series of cell signaling systems, which can cause an increase in cellular ROS, RNS, and LPP, and activate the inflammatory prostaglandin reactions. By increasing the activity of inducible nitric oxide (NO) synthetase, glutamate increases intracellular NO, which in the presence of increased levels of superoxide can generate high levels of peroxynitrite. Peroxynitrite is very toxic to mitochondria energy-producing enzymes. Reducing cellular energy production has been shown to greatly magnify excitotoxicity to a degree where even physiological levels of glutamate can become excitotoxic [148].

Gaba in Autism

Gama amino butyric acid acts as an inhibitory neurotransmitter, during the perinatal period it depolarizes targeted cells and triggers calcium influx. GABA-mediated calcium signalling regulates a number of important developmental processes which include, cell proliferation, differentiation, synapse maturation, and cell death [149]. A dysfunction of the GABAergic signaling early in development leads to a severe excitatory/inhibitory (E/I) imbalance in neuronal circuits, a condition that may account for some of the behavioral deficits observed in patients with autism [150]. There is abundant evidence of GABAergic dysfunction in autism including: (1) Gene association studies with linkage to a number of genes for GABAergic signaling molecules with increased risk of autism; (2) Reduction of GABA binding sites; (3) Reduced expression of glutamic acid decarboxylase (GAD) 65 and 67 kDa proteins and Mrna which are responsible for the conversion of glutamate to GABA; and (4) Altered expression of GABAA and GABAB receptor subunits in brains of subjects with autism [151-

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159]. An increasing body of evidence suggests that a down regulation of GABAergic function is critical in autism associated epilepsy. Quantitative autoradiographic studies examining the density and distribution of GABAergic receptor subunits indicated a down regulation of GABAergic function in the hippocampus of autism patients with seizures [160].

The 50% reduction in GAD65/67protein levels was reported in the cerebellum and parietal cortex of ASD patients [156]. Reduced levels of GAD67 and GAD65 mRNAs were also detected in Purkinje cells and dentate nuclei neurons in the cerebellum from ASD [161].

Figure 2: Neurotransmitters in Autism.
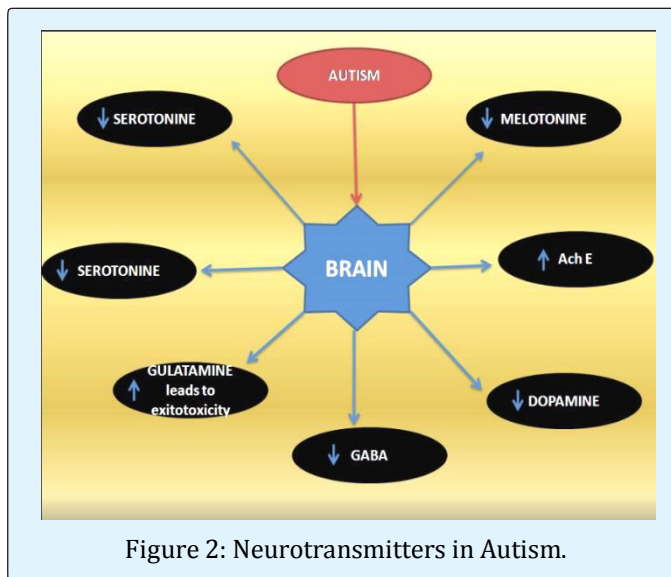
The level GABA, glutamate/GABA and glutamine/glutamate ratios are significantly lower in patients with autism compared to normal controls, thus suggesting a possible abnormality in the regulation between GABA and glutamate that might lead to excitotoxicity [162,163].

Acetylcholine and Cholinergic Receptors: Acetylcholine (ACh) is implicated in various neurological processes such as plasticity, cognition, memory, release of other neurotransmitters and so on, especially in the central nervous system [164,165]. The receptor binding (M1) and nicotinic receptors subunits are low in autistic subjects, which indicate a specific abnormality in cholinoceptive function, since the M1 receptor is located post synaptically. The binding abnormality reflected a low number of receptors. This could be related to epilepsy, which occurs in up to 40% of autistic children [166]. Along with, decreased choline peak was observed in the gray matter and temporal lobe of autistic patients. All of

these studies implicate that ASD patients may have dysregulated cholinergic system in the brain [167].

Brain regions & Neuropathophysiology in Autism

Cerebellum & Autism: The cerebellum comprises 10% of total brain volume, termed the "little brain," but contains more neurons than the rest of the brain and has the highest cell density of any brain area, approximately four times that of the neocortex [168]. Although many regions have been found to be abnormal in the postmortem autistic brain, one of the most consistently described abnormal structures has been the cerebellum and regions related to it [169]. Histopathological changes in the cerebellum have been observed in almost all postmortem brains of autistic individuals. The most consistent neuropathological finding in autism is the loss of Purkinje cells (PCs) [170,171]. Reduced packing density of PCs and reduced PC size [172], have been reported in autistic brains. Further observed cerebellar pathology in ASD includes a reduction of GCs and hypertrophy and atrophy of cerebellar nuclei [173,174]. Cerebellar involvement in coordinated movements has been well described [175], and previous studies indicates that the cerebellum plays an important role in non-motor functions as well [176]. The cerebellum is central in a wide range of functions sometimes found to be impaired in autism, including timing and coordination of movement, motor learning, evaluation of the match between intention and action, predictive learning, environmental exploration, behavioral inhibition, attention, and visual orienting. In particular, the cerebellar vermis is associated with modulation of limbic functions including emotion, sensory reactivity, and salience detection. The cerebellar hemispheres have been linked to several higher order cerebral functions including language, working memory, planning, and behavioral sequencing [177]. Numerous imaging studies have reported cerebellar hypoplasia in autism, specifically smaller cerebellar vermal lobules VI and VII which is associated with ASD symptoms, including reduced exploration and increased stereotyped and repetitive movements. Voxel-based morphometry studies have reported both increases and decreases in cerebellar grey matter and white matter [178-180]. Further analysis of brain alterations seen in patients with autism reveal changes to the acetylcholine (ACh) system in both the cerebellum and forebrain [181]. In addition, there was a 65–73% reduction in nicotinic receptor binding in the frontal and parietal cortical areas that receive connections from the cerebellum [182]. Taking into consideration that about 30–40% of autistic patients have been diagnosed with a seizure disorder, perhaps these

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alterations in cerebellar and/or forebrain neurophysiology are responsible for the stereotyped behaviors as well as the seizures seen in autism spectrum disorders [183]. Some studies demonstrate that cerebellar lesionsalone, without accompanying lesions of the basal forebrain cholinergic system, alter the exploration behavior of adult rats, this reduction of exploration behavior is due to reductions in intracerebellar inhibition that is mediated via Purkinje cells, leading to decreases in inhibitory behavioral control [184].

Cerebral Cortex & Autism: Several studies showed that impaired maturation of the GABAergic circuitry results in an immature structure and function of the cerebral cortex, that remains more plastic and sensitive to alterations in sensory inputs [184,185]. A 50% reduction in GAD65/67 protein levels was reported in the cerebellum and parietal cortex of autism patients [186]. $GABA_B$ receptors were also reduced in restricted regions of the cerebral cortex in autism patients [187]. Some have demonstrated reductions in functional connectivity [188]. There were weaker connectivity reported in most of the studies was between the prefrontal cortex and relatively posterior brain areas. Poor prefrontal-posterior coordination can affect higher-level processing, and may underlie the difficulty in cognitive, social and language processing witnessed in autism [190]. There were significantly higher microglial densities in the subjects with autism compared to the control subjects, and that this change in microglial density is widespread throughout the cerebral cortex in autism [191]. In autism there are significantly increased cytokines in frontal cortex and elevated levels of cytokines in the cerebrospinal fluid compared to control subjects and there is evidence for immune system dysfunction in the development of autistic children [191,192].

Hippocampus & Autism: Emerging evidence especially implicates the hippocampus as being involved in modulating contextually adequate emotional behavior, social behavior, and aggression in addition to its role in cognitive functions [193-195]. Systematic survey of the forebrain in infantile autism has shown reduced neuronal cell size and increased cell packing density confined to the limbic system [196]. There are several neuropsychiatric disorders are associated with altered social endophenotypes, these findings raise the possibility that CA2 dysfunction may contribute to behavioral changes. This possibility is supported by findings of a decreased number of CA2 inhibitory neurons in hippocampus and altered vasopressin signalling in autism [197].The GABAergic system has emerged as a potential candidate

because some studies have found a statistically significant reduction in the density of benzodiazepine binding sites and $GABA_A$ receptors in the hippocampus. The neuropathological findings of the decreased numbers of GABAergic Purkinje cells and altered cerebellar nuclei suggest that this deficit in the GABAergic system may be widespread in the autistic brain [198].

Recently, an increasing number of reports support the hypothesis that immune dysfunction plays a role in autism [199]. It was determined IgA affects the synaptic plasticity of rat hippocampal slices. The results show that LTP decreases are observed in hippocampus isolated from both normal rats perfused with this antibody and hippocampus isolated from animals previously inoculated with this autoantibody and perfused with artificial cerebrospinal fluid (ACSF) alone [200].

Oxidative Stress & Autism

Oxidative stress is known to be associated with premature aging of cells and can lead to inflammation, damaged cell membranes, autoimmunity, and cell death. The brain is highly vulnerable to oxidative stress due to its limited antioxidant capacity, higher energy requirement, and high amounts of unsaturated lipids and iron [201].

Figure 3: Role of oxidative stress in Autism.
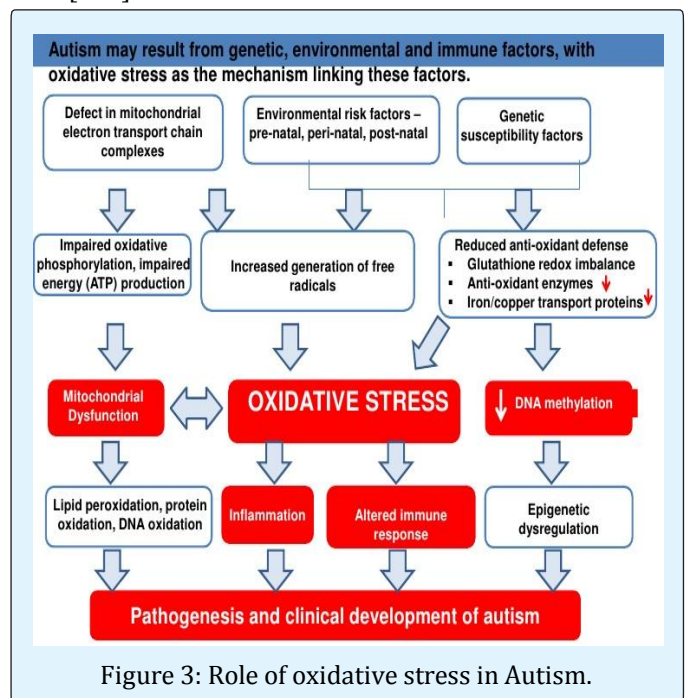
The brain makes up about 2% of body mass but consumes 20% of metabolic oxygen. The oxidative stress in autism could result from (1) the exposure to high levels of environmental pro-oxidants such as pesticides or

mercury (Hg), (2) the inability to metabolize and clear toxicants such as heavy metals from the system, (3) decreased internal antioxidant defense mechanisms, or (4) increased sensitivity to oxidative stress [202-211]. The hypothesis that reactive oxygen species (ROS) play an important role in autism as well as other psychiatric disorders remains speculative and there have been studies to test this hypothesis [212]. ROS including superoxide anion radical (O_2), hydroxyl radical (SOH), hydrogen peroxide (H_2O_2), singlet oxygen ($1O_2$) and nitric oxide (NOS) may lead to cellular injury when they are generated extremely or the antioxidant defense systems are destructed [213]. It was reported that lipid per-oxidation is increased in the plasma of children with autism as compared to their developmentally normal, non-autistic subjects. Malonyldialdehyde (MDA) is an end product of peroxidation of polyunsaturated fatty acids and related esters, and is, therefore, used as a marker of lipid peroxidation [214]. Methylation has an important role in the synthesis of myelin basic protein, an essential component that confers compactness to myelin. This is a critical step because the correct synthesis and assembling of myelin are fundamental in the development of the central nervous system [215]. In addition, decreased DNA methylation increases expression of genes under the negative influence of methylation, disrupting epigenetic silencing of chromosomal regions linked to autism and leading to developmental delay, deficit in attention, and neuronal synchronization, which are typical hallmarks of autism [216]. Several lines of evidence have demonstrated that patients with autism show the decreased levels of main scavenger enzymes, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px), in serum. In addition, oxidative stress levels in the cortex and the cerebellar vermis are also elevated. A proposal has been made that an elevation of oxidative stress in parts of the brain can impair or disturb brain development resulting in the clinical manifestation of autism [14].

Immune Dysregulation & Neuroinflamation in Autism

A common finding is an elevated number of auto antibodies that react against the brain and central nervous system in children diagnosed with autism when compared to suitable controls [217]. Maternal immune activation (MIA) is regarded a principal nongenetic cause of autism. Animal models of MIA exhibit strong face and construct validity for human autism. Importantly, offspring of immune-activated mothers exhibit the cardinal diagnostic symptoms of autism; in mice, MIA offspring exhibit decreased number and quality of ultrasonic vocalizations, as a primary mode of communication, in addition to altered olfactory communication, impaired social interactions, and elevated repetitive marble burying and self-grooming, among other autism-related behavioral abnormalities [218]. It is also reported that MIA induces activation of microglia in the fetal brain and alters neurogenesis [219]. There are several immune-related environmental and genetic risk factors found to increase autism risk, emerging evidence highlights a role for postnatal immune dysfunction in the clinical manifestation of autism symptoms. Striking immune abnormalities are seen in the brains and periphery of autistic individuals [220]. It was reported that a histologic analysis of the brain tissue of children diagnosed with autism showed signs of classic inflammation in the areas where excessive growth was registered, thus demonstrating an involvement of astroglial and microglial cells with no lymphocyte infiltration or immunoglobulin deposition in the central nervous system (CNS) [221,222]. A relatively well-replicated pathology observed in postmortem brains from autism patients is increased microglial abundance and activation [223]. It is of great interest that a numbers of studies have demonstrated abnormalities in innate immune function in autism. Significant findings include alterations in natural killer (NK) cell activity [223]. In circulation, the numbers of NK cells are 40% higher in children with autism compared with controls [224]. Dendritic cells serve a central role in many immune functions [225]. They are highly phagocytic and express many innate pattern-recognition receptors that capture pathogen associated molecular pattern molecules (PAMPs) on microbes or damage-associated molecular pattern molecules (DAMPs) of endogenous tissues. Dendritic cells undergo maturation steps, after binding of these ligands/antigens, that increase mobility for migration, express chemokine receptors for homing to lymphoid organs, produce chemokines to recruit other immune cells, up regulate MHC class II molecules and co-stimulatory molecules for priming of naïve T cells or stimulation of effectors T cells and secrete large quantities of cytokines that polarize or modulate neighboring immune cells [226-228]. The release of cytokines such as TNFa from dendritic cells may also reduce mitochondrial function that has been associated with autism [229]. Data from the current study shows that there are increased circulating frequencies of blood myeloid dendritic cells in young children with autism [230]. There are also several lines of indirect evidence that suggest altered B-cell dysfunction is present in individuals with autism. The primary role of B-cells is the production of immunoglobins against pathogens [231]. In autism, lower circulating levels of IgA have previously been reported [232]. Reduced production of the IgM and

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IgG classes of immunoglobins has been reported, with lower levels found to correlate with more aberrant behaviors [233].

It also suggests that inflammation of the CNS may be important in autism. This is supported by a study finding evidence of neuroinflammation in the post-mortem brain including activated microglia astrocytes. In autism neuroinflammation is observed, these findings include prominent microglia activation and, increased inflammatory cytokine and chemokine production, including interferon (IFN)-c, IL-1b, IL-6, IL-12p40, tumor necrosis factor (TNF)-a and chemokine C–C motif ligand (CCL)-2 in the brain tissue and cerebral spinal fluid [220,223]. Cytokines are proteins that control the intensity, duration, and type of immune response. However, cytokines are also involved in brain development and synaptic functions including processes of differentiation, migration, proliferation, and behavioral impairments [229,234]. Poor communication and impaired social interaction seems associated with elevated levels of cytokines [235]. Many of these cytokines are induced by the activation of the NF-κB transcription factor, a critical factor in inflammation and apoptosis, which is found at increased levels in peripheral blood mononuclear cells in autism. Increased levels of TNF-α and its capacity to block synaptic communication are the most consistent and typical finding in autism brain, cerebrospinal fluid and blood cells. Increased TNF-a production was also associated with increased stereotypical behaviors a hallmark symptom of autism [235,236]. A higher number of monocytes and increased plasma concentrations of IL-8, which indicates abnormal inflammatory activity in children with autism [237].

Amygdala & Autism: Amygdala is sensitive to environmental signs of emotional and social significance. The social status has been found to be linked to the degree of amygdala activation [238]. Dysfunction of the amygdala has been found to be related to disorders of fear processing, anxiety, and even social behaviors [239,240]. There has been particular interest in the role of the amygdala in the development of autism. Emotion and facial processing has also been noted in autistic individual due to altered amygdala activation [241]. Structural MRI studies have provided evidence for abnormal amygdala development in autism. In young children with autism, ages 2–5 years, there is substantial evidence for abnormal amygdala enlargement relative to typically developing controls [242]. Postmortem have reported an increased cell packing density and smaller neuronal size in limbic regions including the amygdala in autism [243]. Physiological activation of the basolateral nucleus of the amygdala (BLA) in rats, by either blocking tonic GABAergic inhibition or by enhancing glutamate or the stress-associated peptide corticotropin releasing factor mediated excitation, causes reductions in social behaviors [244]. Previous studies reported both amygdala hyperactivation and hypoactivation triggered by faces [245,246]. It was hypothesized that individuals with autism would show reduced eye movements toward the eyes along with decreased amygdala activity when starting fixation on the mouth (in accordance with reduced orientation) and/or enhanced eye movements away from the eyes accompanied by increased amygdala activity when starting fixation on the eyes (in accordance with avoidance), compared with controls [247]. Grey matter density in the junction area between the amygdala, hippocampus and entorhinal cortex on the medial aspect of the rostral temporal lobe was found to correlate with ratings of autistic behavior. One potential mechanism is decreased amygdala habituation. Habituation refers to decreased neural response with the repeated presentation of a stimulus [248,249]. The ventromedial prefrontal cortex (vmPFC) is thought to be involved in amygdala habituation. Animal models have shown that the vmPFC regulates amygdala activity by signaling inhibitory interneuron's in the amygdala [250]. In humans, stronger vmPFC amygdala connectivity predicts greater amygdala habituation [251]. Moreover, the density of serotonin receptors in the medial PFC, part of the pathway providing negative feedback to the amygdala, correlates with amygdala habituation in healthy adults [252]. Therefore, abnormal functioning of this circuit may relate to decreased amygdala habituation in autism. Using eye-tracking methodology, some studies have found reduced eye contact in autism [253]. Individuals with autism have also been shown to have abnormal amygdala activation when fixating the eyes of faces [246], buttressing the hypothesis that one of the key neural structures responsible for impaired eye gaze in autism is the amygdala. The extensive projections from the basal and accessory basal nuclei of the amygdala to the ventral striatum also provide further theoretical rationale for an amygdala involvement in restricted repetitive behavior (RRB) [254].

Basal Ganglia & Autism: There is increasing evidence that autism is associated not only with impairments in development of social and communicative skills but also with impairments in motor skill development, including clumsy gait, poor muscle tone, and imbalance [255,256]. There is some evidence that the basal ganglia are important for postural changes necessary to initiate and maintain locomotion [257]. The basal ganglia surround the diencephalon and are made up of five subcortical

nuclei: globus pallidus, caudate, putamen, substantia nigra, and the subthalamic nucleus (STN) of Luys [258]. The finding that motor dysfunction may underlie some of the core features of autism [259]. Some findings are also particularly interesting as the basal ganglia are implicated in cognitive and motor control and have been linked specifically to repetitive and restricted behaviours in autism [260].

Mitochondrial Dysfunction & Autism: Most neuronal ATP is generated by mitochondrial oxidative phosphorylation (OXPHOS), neurons critically depend on mitochondrial energy metabolism and oxygen supply to execute the complex processes of neurogenesis, neurotransmission and synaptic plasticity [261]. By generating energy and regulating subcellular calcium and redox homoeostasis, mitochondria play an important role in controlling fundamental processes in neuroplasticity, including neural differentiation, neurotransmitter release and dendritic remodelling [262]. Mitochondrial dysfunction can result in certain clinical phenotypes such as developmental delay, hypotonia, ophthalmoplegia, muscle weakness, cardiomyopathy and lactacidosis [263] and affects mainly the highly oxidative tissues including brain, heart, muscle, kidney, as well as the metabolic systems playing a major role in diabetes, obesity, and in a range of neurodegenerative and neurodevelopment diseases [264]. Mitochondrial dysfunctions play a central role in the etiology of autism. Association between mitochondrial dysfunction and autism was first suggested over 20 years ago; [265] and it was hypothesized that individuals with autism may have an abnormality in carbohydrate metabolism, and autism may be a disorder due to impaired mitochondrial function and abnormal brain bioenergetics [266]. Mitochondrial dysfunction can result in the relative increase in the excitatory-to-inhibitory ratio observed in autism [267]. Recent evidence has unveiled an alteration of mitochondrial aspartate/glutamate carrier 1 and calcium homeostasis and impairment in the mitochondrial electron transfer chain in the pathogenesis of autism [268]. Biomarkers of fatty acid elongation and desaturation, namely poly-unsaturated long-chain fatty acids (PUFA) and/or saturated very long chain fatty acids (VLCFA) containing ethanolamine phospholipids, were significantly elevated in autism, as a consequence of impaired mitochondrial beta Oxidation [269]. Mitochondria have an important role in lipid metabolism, previous reports of abnormalities in lipid metabolism and lipid peroxidation in some individuals with autism could be due to mitochondrial dysfunction [270]. It was also reported that, brain region-specific deficit in the protein expression of ETC complexes (I, II, IV & V) in the cerebellum, and cortices from frontal and temporal regions of the children with autism [271].

Toxin Models of Autism

There has been growing interest in the possible involvement of a variety of environmental agents, such as chemical toxins and infectious agents which could act during critical periods of pre and early postnatal development [17]. These observations have led to the development of a number of animal models based on exposing rodents to thalidomide or valproic acid during the prenatal period [18]. One relatively new potential autism model is the propionic acid (PPA) rodent model developed in our laboratory [272,273]. In this model, it was hypothesize that PPA, and/or related enteric fatty acids, may be candidate environmental factors involved in the pathophysiology of some types of autism.

Propionic Acid & Autism: Propionic acid (PPA) is a short chain fatty acid formed endogenously in the human body as an intermediate of fatty acid metabolism and a metabolic end product of enteric gut microbiota such as clostridia and propionibacteria [21,22]. Researchers have demonstrated that PPA intraventricularly infused to rats provides a suitable animal model to study autism. Being a weak organic acid, PPA exists in ionized and nonionized forms at physiological pH allowing it to readily cross lipid membranes, including the gut–blood and blood–brain barriers.PPA and other short-chain fatty acids (i.e. butyrate and acetate) [272,273], affect diverse physiological processes such as cell signaling, neurotransmitter synthesis and release, mitochondrial function, lipid metabolism, immune functions, gap junctional gating, and modulation of gene expression through DNA methylation and histone acetylation [274]. Initial studies using this rodent model revealed that repeated brief infusions of PPA into the lateral cerebral ventricles (i.e. AP 1.3 mm, ML 1.8 mm, DV 3.0 mm) of adult rats produced behavioral, biochemical, electrophysiological and neuropathological effects consistent with those seen in autism[275]. PPA through oxidative mechanisms inhibits Na+/K+ ATPase [29,30] and increases glutamate receptor sensitivity which can enhance neural depolarization leading to neural hyper excitability in brain regions linked to locomotor activity.

Mitochondrial dysfunction has been well established to occur and play an important role in the pathogenesis of autism [8]. Preliminary magnetic resonance spectroscopy studies showed decreased synthesis of ATP and a disturbance of energy metabolism in the brain of

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individuals with autism.PPA is also capable of altering dopamine, serotonin, GABA and glutamate systems in amanner similar to that observed in autism [25-28].
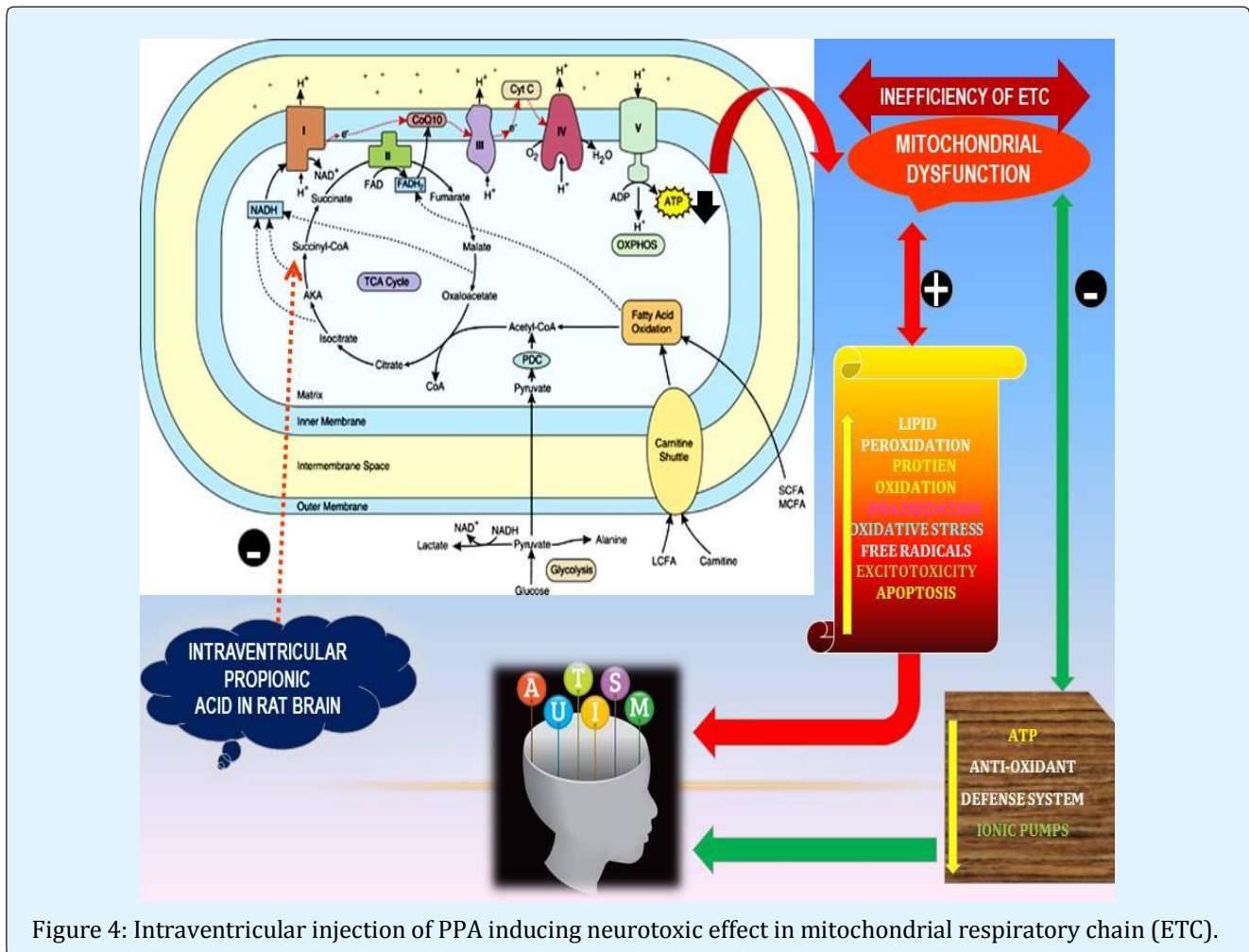

Figure 4: Intraventricular injection of PPA inducing neurotoxic effect in mitochondrial respiratory chain (ETC).

Valproic Acid, Thalidomide & Autism: Valproic acid or sodium valproate induced, is also a well established model for autism in rodents such as rats and mice, to evaluate exact pathophysiological mechanism and therapeutic drugs [276]. In some reports, administration of VPA on 12.5 day of gestation developed autism manifested by lowered body weight gain, impaired olfactory discrimination, reduced swim performance, delayed eye opening and behavioural aberrations such as decreased sensitivity to pain, increased locomotor activity in novel environment, associated with decreased exploratory activity, increased anxiety in elevated plus maze, decreased social explorations in both adolescence and adulthood period [277].

However, Thalidomide, an anti-nausea drug used by pregnant women between 1957 and 1962 was shown to be linked to a marked increase in the incidence of autism in their offspring [278].

Cyclic Neucleotides

Cyclic nucleotides have been implicated as intracellular messengers mediating the action of several neurotransmitters in the central nervous system (CNS) [279]. In the normal physiological conditions, cyclic nucleotides regulates many biological processes such as cell growth and adhesion, energy homeostasis, neuronal signalling and muscle relaxation. The role played by cyclic nucleotides extends not only to the regulation of metabolic processes but also to cell morphology and differentiation [280]. Secondary messengers subsequently activate target enzyme Protein kinase A (PK$_A$) that activate cyclic AMP responsive element binding

protein (CREB), to promote gene transcription which plays an important role in learning and memory function especially long term memory following new protein synthesis and nourishment of nervous system [281,282].

Cyclic AMP& Brain: cAMP (Cyclic Adenosine Monophosphate) an intracellular "second" messenger that is activated in response to certain hormones which are "first" messengers, such as epinephrine, because they cannot pass through the cell membrane. The balance of cAMP signaling is essential to multiple cellular processes, including immune function, growth, differentiation, gene expression and metabolism [283]. Phosphodiesterase (PDE) and adenylyl cyclase (AC), these are two apposite enzymes which regulates the activities of second messenger (cAMP) [284]. It was identified that AC as a source of cAMP inside mitochondria. Some evidence has suggesting that cAMP-mediated phosphorylation of mitochondrial enzymes plays a role in oxidative phosphorylation (OXPHOS) regulation and it is decreased by AC inhibition [284]. BDNF (brain derived neurotropic factor) is dependent on cAMP, it is regulates the expression of BDNF, that regulates neuronal survival [285]. Stimulation of the CREB/CRE transcriptional pathway in neurons depends on the activation of MAP kinase. The activation and nuclear translocation of MAP kinase is regulated by cAMP. It can be either pro-apoptotic or anti-apoptotic [286,287]. cAMP regulating plasticity as well as maintaining the stability of synapses. Increasing the concentration of cAMP delays induced cell death. cAMP cascade modifies the neural connectivity and synaptic strength [288].

cAMP Response Element Binding Protein (CREB) & Brain: CREB is a 43 kDa basic/leucine zipper transcription factor, including activating transcription factor 1 (ATF1), ATF2 (also known as CREBP1), ATF3 and ATF4, which bind to cAMP-response-element (CRE) promoter sites on target genes. It is highly conserved and expressed in most tissue types [289,290]. The transcriptional activation of CREB is due to phosphorylation of serine 133 by a serine-threonine kinase. CREB regulates the expression of several genes involved in metabolism, signaling, proliferation, differentiation and survival [290]. It also regulates many aspects of neuronal functioning, including neuronal excitation, development and long-term synaptic plasticity [291-293]. CREB plays an important role in integrating intracellular cAMP and calcium signaling as well as responses to neurotrophic factors [294]. CREB may play a beneficial role in Rubinstein Taybi-syndrome (RTS), is a rare human genetic disorder characterized by mental retardation and physical abnormalities loss [295]. An

NGF-mediated retrograde signal may increase expression of Bcl-2 through phosphorylation and activation of CREB. CREB and Bcl-2 are both necessary and sufficient for survival of sympathetic neurons, and CREB is a mediator of NGF-dependent gene transcription [296]. CREB is also plays a key role in regulating neuronal survival and differentiation in response to other neurotrophic factors BDNF, FGF and IGF-1 [296]. CREB is also crucial for memory formation. Synaptic restructuring, believed to be crucial for memory formation, seems to be dependent on CREB transcription [297]. Activation (phosphorylation) of CREB seems to be a crucial event in the neuronal growth and development and in cognitive functioning. Inhibition of the component of the cAMP/PKA/CREB pathway is known to suppress CREB phosphorylation [289]. CREB phosphorylation may be a pathological component in neurodegenerative disorders. It may play a role in Alzheimer's and Hungtington's disease.

CREB Activation: The phosphorylation of CREB can be triggered by a variety of signaling processes, including an increase in intracellular Ca^2 via activation of voltage- or ligand-gated channels such as NMDA receptors, an increase in cAMP via activation of G protein coupled receptors or activation of receptor tyrosine kinase by growth factors.
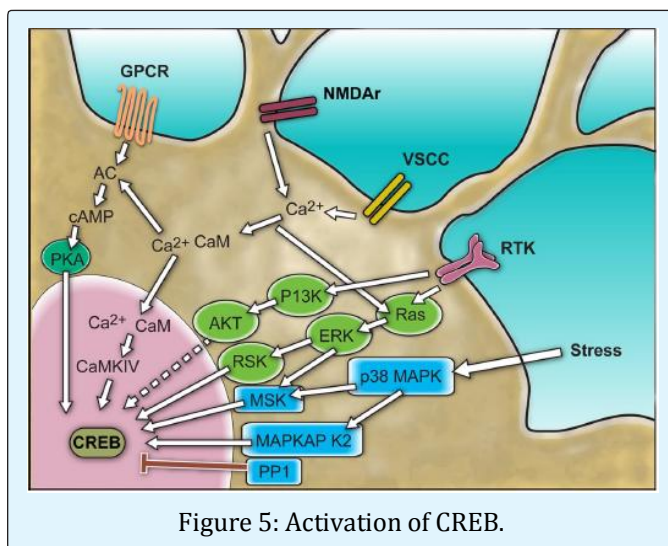
Figure 5: Activation of CREB.

The most common and best elucidated is the cAMP-PKA pathway. Extracellular signals (ex: Hormones and neurotransmitters) activate heterotrimeric G-proteins, that directly stimulate AC, which can then catalyze the production of cAMP. cAMP then leads to the activation of PKA, which dissociates into active catalytic subunits which can diffuse into the nucleus and phosphorylated CREB [298, 299]. Additionally, growth factors can

stimulate their respective receptors, which can lead to stimulation of RAF and the downstream kinases RAS, MEK and ERK. Activated ERK can them stimulate RSK to translocate to the nucleus to phosphorylate CREB. Furthermore, intracellular Ca++ can stimulate the PK_A pathway (through calmodulin) or activate members of the Calmodulin-dependent kinase family (CcamK) which can phosphorylate CREB directly. Once activated, CREB controls the transcription of various important genes [300].

Role of CREB in Neuronal Functioning: Despite expression of CREB in different tissues, it plays a key role in the functioning of the nervous system**.** CREB-dependent expression of genes plays an important role in both the developing and mature nervous system. Three processes are involved in recovery of neural function: synaptic plasticity, neurogenesis and axon growth. The CREB and CRE-mediated system is important for all three processes. Target genes of CREB include many encoding metabolic enzymes, transcription factors, neurotransmitters, cell cycle-related proteins, cell survival-related molecules, growth factors, immune regulatory proteins and structural proteins [297].

Figure 6: Role of CREB in neuronal functioning.
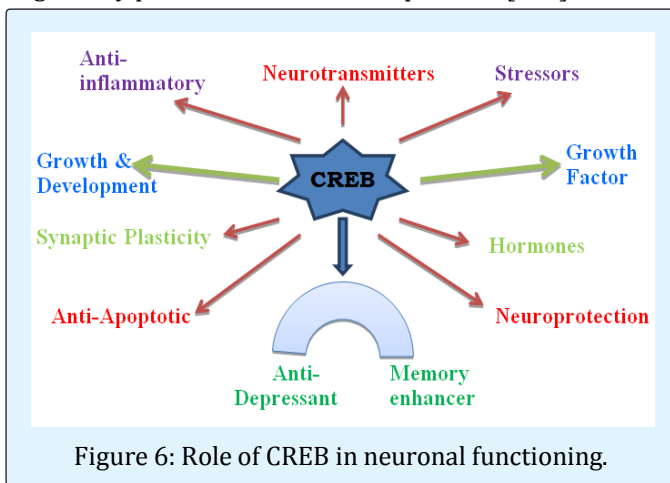
The whole information which is given above cAMP well implicated in cognitive functioning and the levels of this cyclic neucleotide can be raised through selective activation on enzyme AC [301]. There is least availability of selective activation of AC and among these; so far only limited reports suggest beneficial effects of FSK in various *in-vitro& in-vivo* preclinical studies.

Forskolin (Coleus Forskohlii)

Coleus forskohlii known as phashanabedi (telugu) a medicinal plant found in the Indian subcontinent is widely used in the Indian system of medicine. Forskolin (FSK) (also known as Colonels) is labdane diterpene that is obtained from the tuberous roots of *Coleus forskohlii* which belonging to the family of Lamiaceae [302,303]. *Coleus Forskohlii* is one of the world's most researched plant in which FSK is believed to be the plant's most active constituent. *C. forskohlii* has been used as an important folk medicine in India. *C. forskolii* is a perennial herb and grows wild in arid and semi-arid regions of India, Nepal and Thailand; the roots have long been used in Ayurvedic medicine [304]. In traditional medicine, C. forskohlii is commonly used in different countries for various health disorders including cardiovascular diseases, hypertension, asthma, glaucoma and Alzheimer's disease [305-308]. Its further use in promoting lean body mass, treating mood disorders and its anticancer activities is well known [309].

Medicinal Properties of Forskolin: Traditionally, the roots have been used as condiments in pickles, for preparation of pickles. Forskolin has positive effect against a wide range of conditions such as asthma, glaucoma, hypertension, hair loss, cancer, and obesity [310-314]. *C. forskohlii* extract (standardized to contain 95% forskolin) is potentially useful in skin care formulations, particularly as a conditioning age. In traditional Indian systems of medicine, the roots of *C. forskohlii* are used as a tonic. Other therapeutically relevant properties include anthelmintic action and efficacy in the management of skin infections and eruptions. The plant is also used traditionally in veterinary practice [304]. Essential oil in tubers of this plant has potential uses in food flavouring industry and can be used as an antimicrobial agent and has very attractive and delicate odour with spicy note. A labdane diterpenoid is considered the active secondary metabolite because of its ability to activate the enzyme Adenyl cyclase (Ac) thereby increasing the intracellular level of cAMP and leading to various physiological effects [315]. FSK is shown to exert a 6-400 fold increase in levels of cAMP. Cyclic AMP is a "second messenger" hormone signalling system as its synthesis triggers the action of various hormones, enzymes and other biological activities that have profound effects on local cells, as well as systemic effects, in some instances, on the entire body [316]. FSK by passes the adrenoreceptors, increasing cAMP levels directly, thereby stimulating lipolysis. FSK has also been shown to counteract the decreased response of fat cells to epinephrine, associated with aging. FSK also accelerates lipolysis through the activation of hormone-sensitive lipase [317]. It is primarily via the increased synthesis of cyclic AMP that *C. Forskohlii* may exert its medicinal influences on a significant number of common health conditions.

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S.No	P'cological Activity	Mechanism of action	Ref.No
1.	Anti-Depressant	FSK stimulated AC activity in rat brain and leads to enhancement of the coupling between stimulatory GTP-binding protein (G protein) and AC catalytic molecules	318
		FSK stimulates AC and regulates brain-derived neurotrophic factor (BDNF) and TrkB expression in the rat brain	319
2.	Anti-Alzheimer's	FSK induced a bipolar neuron-like cell morphology and it enables neurogenin-2 (Ngn2) to convert human fibroblasts into cholinergic neurons	320
		Neuronal differentiation of adult rat neural progenitor cells (NCP's) was achieved	321
3.	Anti –cancer	Restoration of PP2A activity with forskolin that inhibit Akt and ERK activity, block proliferation and induce caspase-dependent apoptosis in AML cell lines.	322
		Forskolin inhibited the *in-vivo* leukemogenesis of imatinib sensitive and resistant BCR/ABL+ 32Dcl3 cells in mice	323
4.	Antispasmodic activity	increase of cAMP inhibit cramping or smooth muscle contraction	324
5.	Anti-Glaucoma	Stimulates Adenylate cyclase which stimulates the ciliary epithelium to produce cyclic adenosine monophosphate (cAMP) that results in decreased aqueous humor inflow there by decrease in IOP	325
		Reduction of intra ocular pressure	326
6.	Cardio protective	It reduces diastolic blood pressure without increasing myocardial oxygen consumption.	327
	Amelioration of Mitochondrial dysfunction in cardiomyopathy	Reduction of I_{Na} (cardiac Na+ current) and overproduction of mitochondrial ROS in deoxycorticosterone acetate (DOCA) mouse myocytes by activating PKA and PKC	328
8	Anti-Asthmatic	Forskolin activation of cAMP inhibits human basophil and mast cell degranulation, resulting in subsequent bronchodilation	329
7.	Anti-Psoriasis	Decreased cGMP levels that are associated with cell proliferation and thus decrease cell divison.	330
		Normalizing the cAMP /cGMP ratio.	331
8.	Hepatoprotective activity	Repair of hepatic tissue damage, normalization of inflammatory hepatic and necrosis	332
		Forskolin increases cAMP accumulation, and therefore stimulates lipolysis.	333
9.	Anti- inflammatory	Reduction in the level of Interleukin-1β, 6 and 8	334
		Over-expression of Tank binding kinase1 (TBK1) reduced phosphorylation of Hormone sensitive lipase (HSL) in response to FSK	335
		Inhibit mast cell degranulation	336
10.	Anti-Diabetic activity	FSK predominantly decreased basal glucose in healthy rats and attenuated the severity of hyperglycemia in diabetic rats	337
		FSK increase intracellular cAMP, which, together with the increase in ATP, enhance the priming of insulin granules	338

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11.	**Anti-platelet Aggregation**	Antagonizes the action of platelet-activating factor (PAF). Reduction in the extent of platelet aggregation	339
		Induced a partialdeaggregation of ADP- or collagen-aggregated human platelets	340
12.	**Inhibition of human neutrophil degranulation**	cAMP mediated Phosphodiesterase inhibition.	341
	Anti-Histaminic activity	Reduction in the histamine release from human basophiles and mast cells by modulating the release of mediators of the immediate hypersensitivity reaction, through activation of AC	342
13.	**Smooth muscle relaxant**	Increase both the cytosolic Ca^{2+} concentration and the cytosolic NO concentration ([NO]c) in the endothelial cells leads to cause vasodilatation	343
		Increases uterine smooth muscle AC	344
14.	**Hydrodynamic alterations in collecting tubule**	FSK resulted in increase in osmotic water flux and hydraulic conductivity of the rabbit cortical collecting tubule	345
	Anti-cystic fibrosis	FSK leads to cyst formation in culture media	346

Table 1: Pharmacological action of FSK.

FSK and Brain

FSK Binding Sites: 3H-forskolin has, for example, been found to bind to both a high and a low affinity site in rat brain membranes and the capacity of the high affinity forskolin binding site has been shown to be increased by the activation of N-proteins by guanine nucleotides [345-346]. High affinity [3H] FSK binding sites have been mapped autoradiographically in rat brain area such as caudate-putamen, nucleus accumbens, olfactory tubercle, giobus pallidus, substantia nigra and the hilus of the area dentata and exhibit a markedly heterogeneous distribution [347].

Role of FSK in Brain: FSK may activate Ac by interacting with two sites, one which may be directly located on the cyclase molecule, and the other which is associated with OJ somehow formed by the interactions with the N, protein [338]. FSK, a commonly used activator of Ac, elevates the stimulation-induced release of several transmitters, such as acetylcholine, noradrenaline and 5-hydrdoxytryptamine, from brain or synaptosomes and markedly increasing the rate of conversion of ATP to cyclic AMP [315,348]. FSK directly reduces certain K+-potassium currents in addition to its action on Ac. cAMP could increase the apparent number of Na, K-ATPase sites by either direct or indirect mechanisms. cAMP could increase the number of Na, K-ATPase sites by increasing cell Na + or decreasing K + though there are reports of Na, K-ATPase stimulation that may be independent of cation changes. FSK elevates electrically evoked acetylcholine release in the hippocampus independently of Ac activation [349]. FSK appears to provide a new clue for elucidating the physiological role of cAMP in the synaptic transmission in the sympathetic ganglia. FSK exerts two opposite pharmacological actions at the synapse, i.e. a facilitation of transmitter release at the presynaptic site and a depressant action on nicotinic acetylcholine receptor at the postsynaptic site. FSK reduced the amplitude shock stimulation of preganglionic nerve. FSK induces a reversible AChR desensitization at the junctional and extra junctional regions in rat [350]. FSK, an activator of Ac, could increase transmitter release presynaptically in CA1 neurons. FSK directly stimulates Ac and thereby increases cyclic AMP activity, which is known to influence neurite outgrowth and membrane trafficking in neurons. Increased cyclic AMP activity may have multiple effects on cells including changing the direction of growing neurites and increasing the density of clathrin-coated pits and coated vesicles at plasma membranes coincident with an increased synthesis of clathrin light chain. The cAMP effectors system enhanced by FSK is involved in the release of dopamine from dopaminergic nerve endings in the neostriatum [351-352]. FSK increased dopamine formation in rat striatal slices, rat striatal synaptosomes, rat hypothalamic synaptosomes and bovine retinal slices [353].

Neuroprotective Action of FSK

Fsk against Neuro-Inflammation: An increase in intracellular cAMP levels through FSK to play an important role in modulating the cytokine production. Intracellular cAMP has been reported to depress the accumulation of tumor necrosis factor (TNF-α) an mRNA by inhibiting the transcriptional processes. Elevation of

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intracellular cAMP levels induced by PDE inhibitors, FSK, prostaglandin E2, or cell-permeable cAMP analogue also inhibited the secretion of IL-1b, whereas it increased IL-1b mRNA levels from lipopolysaccharide-stimulated human monocytes. Although the regulatory modality of IL-8 production by cAMP is still unclear and depends on the cell type, enhanced cAMP appears to have favourable effects at least on airway cells by suppressing IL-8 production [354,355]. Therefore, enhanced cAMP levels by have also FSK been recognized to reverse the increased pulmonary microvascular permeability associated with ischemia reperfusion [356].

Forskolin against Neuro-Oxidation: Oxidative stress may play a role in the development and clinical manifestations of autism. Both central and peripheral markers of oxidative stress have been reported in autism. Peripheral markers have included lipid peroxidation levels. Increases in these markers correlated with loss of previously acquired language skills in autism. Furthermore, metabolic markers of oxidative stress have been identified including abnormal levels of metabolites signifying impaired methylation and increased oxidative stress in autism [357]. The oxidative stress in autism may be caused by an imbalance between the generation of ROS and the defence mechanism against ROS by antioxidants. An increase in reactive oxygen species (ROS) results in damage to proteins, DNA, and lipids. Specifically, the interaction between ROS and nitric oxide (NO) results in the nitration of tyrosine residues in proteins and can alter protein conformation and function [358]. Oxidative DNA damage is also considered to play an important role in the pathology of a number of diseases like Parkinson's disease, tardive dyskinesia, metal intoxication syndromes, Down's syndrome, and possibly also in schizophrenia, Huntington's disease, and Alzheimer's disease. Reactive oxygen species including superoxide (O2.–), hydroxyl (.OH), hydrogen peroxide (H_2O_2), singlet oxygen ($1O^2$) and nitric oxide (NO•) can cause cellular injury when they are generated excessively or the enzymatic and nonenzymatic antioxidant defence systems are impaired [359].

Moreover, FSK mediated cAMP/PKA/CREB activation were found to inhibit LPS- and cytokine-mediated production of NO as well as the expression of iNOS, whereas compounds (H-89 and (Rp)-cAMP) that decrease PKA activity stimulated the production of NO and the expression of iNOS in rat primary astrocytes [360-362].
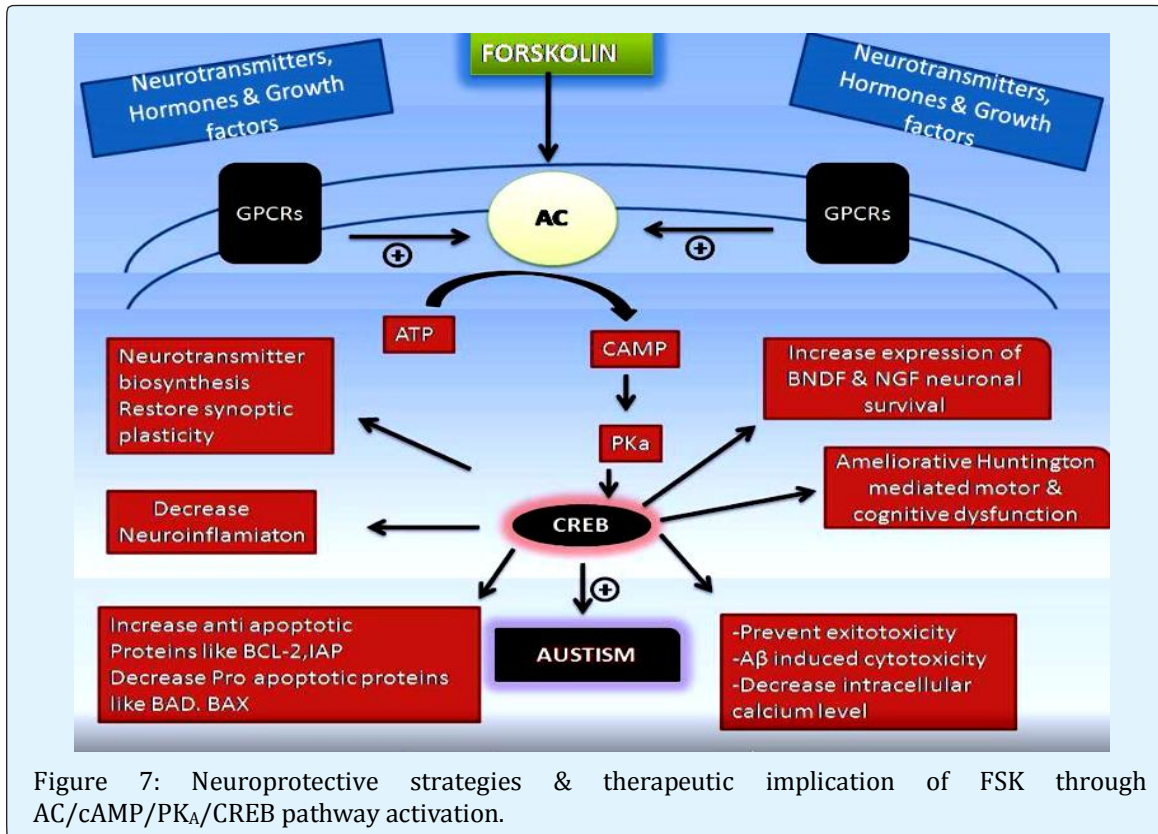
Forskolin against Mitochondrial Dysfunctioning: The brain is strongly dependent on the ATP production of the cell energy-producing organelle, the mitochondrion. There is a large body of evidence involving mitochondrial dysfunctions in ASD. Palmieri and Persico, regarding ASD, oxidative phosphorylation (OXPHOS) in the mitochondrion requires at least 80 proteins, of which only 13 are encoded by the mtDNA, while mitochondrial functioning has been estimated to need the participation of approximately 1500 nuclear genes [333]. Mitochondrial dysfunction is present in the brains of individuals with ASD and may play a role in its core cognitive and behavioral symptoms. Alternatively, mitochondria can be damaged by endogenous stressors associated with ASD such as elevated proinflammatory cytokines resulting from an activated immune system or other conditions associated with oxidative stress. Oxidative stress may be a key link between mitochondrial dysfunction and ASD as reactive oxygen species (ROS) generated from pro-oxidant environmental toxicants and activated immune cells can result in mitochondrial dysfunction. Excess production of free radicals or impaired antioxidant mechanisms may cause oxidative stress: impaired mitochondrial function then leads to further oxidative stress and a vicious negative cycle can ensue. Instead, abnormal functioning appears secondary to excessive Ca2+ levels. Mitochondrial dysfunctioning caused depletion of ATP, that further decrease the level of cAMP [353]. Forskolin, increase in intracellular cAMP, through the phosphorylation of CREB which perform neuroprotective functioning associate with mitochondrial dysfunctioning [363].

Forskolin against Cognitive Dysfunction: Autistic brain which may reflect enhanced cortical plasticity which is defined as the process of microstructural construction of synapses occurring during development and the remodelling of these synapses during learning [364,365]. Enhanced synaptic plasticity triggers a regional reorganization of brain functions that account for both the unique aspects of autism and its variability [366]. Activation of cAMP/PKA has been mainly implicated in stimulating learning and memory. FSK activate cAMP/CREB in hippocampal region [367,368-394].

Conclusion

Summarizing the whole information given above, FSK confirmed a versatile role in autism where it activates the AC/cAMP mediated PK_A/CREB activation (Figure 7) Moreover, on other side FSK act as a co activator in brain that follows the G_S pathway through the activation of D1 receptor. There is least availability of selective AC activation and so far only limited reports suggest beneficial effect of FSK in neurodegeneration animal model.

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Figure 7: Neuroprotective strategies & therapeutic implication of FSK through AC/cAMP/PK$_A$/CREB pathway activation.

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