REVIEW ARTICLE

Impact of thousand-and-one amino acid 2 kinase mediated neuro-differentiation in cerebral cortex and impairment of mirror neuron pathways on autism spectrum disorders

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ABSTRACT

An understanding of how neurons develop their morphology and their distinct physiology is the key to the elucidation of the mechanisms underlying sophisticated cognitive functions in normal and disease conditions. Evidence suggests that neurodevelopmental disorders with delayed onset, such as autism spectrum disorders (ASDs) might be a consequence of aberrant dendritic arborization. This review is dedicated toward the discussion of a new pathway that specifically affects the formation of basal dendrites and axonal projections in cortical pyramidal neurons. With reference to this pathway, the function of thousand-and-one amino acid 2 kinase, in relation to dendrite morphogenesis has been elaborated. Mirror neuron system dysfunction may underlie a self-other matching impairment which has been suggested to account for autism. The hypotheses of deficit an impaired mirror neuron function in autism have now been well supported by studies employing a range of methodologies. However, underlying mechanisms require further exploration to explain how mirror neurons may be involved in attention and metalizing processes. It seems possible that different sub-populations of mirror neurons, distinct in particular anatomical regions of the brain, contribute differentially to social cognitive functions. Mirror neuron networks dysfunction in ASD-affected individuals leading to dampened imitation learning, misguided development of "egocentrism" and even failure to comprehend the intention behind a motor act. While it seems clear that autism is associated with impaired development of embodied aspects of cognition, the ways that mirror neurons contribute to these brain-behavior links are likely to be complex and demands further research.

KEY WORDS: Thousand-And-One Amino Acid 2 Kinase; Autism Spectrum Disorders; Mirror Neuron

INTRODUCTION

Autism is a severe neurobehavioral syndrome, arising largely as an inherited disorder, and is caused by a collection of diseases, which becomes apparent in the 1st years of life.[1]

Autistic phenotype is heterogeneous. However, abnormalities in language and social skills are at its core.[2] As most autistics have IQs lower than 70, autism is often viewed as a type of mental retardation. However, autism is distinguished from other mental retardation syndromes by disproportionately severe defects in language and social skills. Twin studies have shown that autism is a strongly inherited disorder as monozygotic twins co-inherit this syndrome several times more frequently than do dizygotic.[3]

Much of the heterogeneity of autism's expression relates to the heterogeneity of the genetic factors that underlie it. It is known that mutations in different genes can cause autistic-like

syndromes in subsets of children with a variety of genetic diseases including Fragile X syndrome and Rett syndrome.[4] These diseases are caused by genes that are widely expressed in the nervous system.

The following characteristics of the genetic contribution to autism have been identified:[5]

1. Linkage analysis suggests that multiple genes can cause autism alone or in combination with other genes
2. No gene is necessarily a major determinant of autism
3. Genes that cause autism may not do so in all people carrying the same mutation. Differential penetrance may occur if the individual: (i) Hasn't co-inherited other susceptibility genes; (ii) hasn't been exposed to the same environmental insults; (iii) if there is a stochastic contribution to a relevant developmental process.

Studies of monozygotic twins in which one twin is autistic, while the second twin has a much milder expression of the syndrome or is not identified as autistic, have implicated non-genetic sources of variance.[6] Interestingly, the "less autistic" or non-autistic twin has milder impairments in language abilities and social behaviors, and less marked physical differences in the brain regions that support them.

Autism is characterized by a disproportionate disability of an affected individual's language and social skills. Furthermore, monozygotic twins of autistics that do not develop autism nonetheless suffer milder deficits in these specific faculties. It is, therefore, likely that neural systems that subserve these behaviors are at the core of the pathophysiology. In view of these observations, it is reasonable to suggest that efforts to understand autism origin should focus on the development of neural circuits and systems that underlie language processing (such as audition, language comprehension, speech production and verbal memory and cognition), along with social and affiliative behaviors.

NEURAL SYSTEMS IMPLICATED IN AUTISM: PREVIOUS BIOLOGICAL FINDINGS

Abnormal Maturation of Brain in Autism

Since autism is a developmental disorder, there is an associated abnormal developmental trajectory of the brain. There are several important brain maturational events that continue into early adulthood, such as synaptic pruning, elaboration of dendritic arborization, and increased myelination[7] that could impact cortical connectivity. Abnormalities in any of several brain development mechanisms in autism could result in abnormal cortico-cortical connectivity.[8]

Pruning of synapses normally occurs during later stages of neuronal development. It has been postulated that this pruning is compromised in autism.[9] In the typical brain, initial growth and subsequent regression (due to mechanisms like neuronal loss and synaptic pruning) are timed in ways that are presumed to allow activity and experience to support the organization of functional networks.[10] The growth profiles in autism may not support an appropriate balance between maturation and experience. Normal pruning could help eliminate faulty connections and optimize coordinated neural functioning. However, compromised pruning might fail to do so, possibly resulting in some degree of anatomical "overconnectivity" that could either increase or decrease the efficiency of communication among cortical regions. Decreased elimination of neural structures, including apoptosis, axonal pruning, and dendritic degeneration, as well as increased neurogenesis, has been suggested to occur in autism.[11]

It was hypothesized by Frith (2003)[9] that the brain enlargement in autism was linked to abnormal connectivity, brought about by a lack of pruning. He further hypothesized that several behavioral and neural characteristics of autism might be a consequence of the frontal cortex failing to adequately modulate sensory processing. This failure of sensory processing is due to the frontal cortex's reduced connectivity with posterior areas.

Consistent with Firth's hypotheses is the observed fact that enlarged brain size occurs in autism in early stages of development with the enlargement being greatest in the frontal cortex.[12] It is possible that increased brain size during development may critically impact the relative cost and efficiency of short-distance and long-distance cortico-cortical connectivity.[13] Overgrowth gives rise not only to conduction delays but also to greater cell maintenance costs associated with long-distance connections. A compensatory process would thus be a reduction in the proportion of more costly long-distance connections

White Matter (Myelination) Abnormalities in Autism

Integrity of the white matter tracts that carry the information between different brain regions affects inter-regional cortical communication. Connectivity is usually thought of at the level of connections between individual neurons, but the phenomenon of communication among cortical centers in different parts of the brain is enormously affected by the degree of myelination of axons. Myelination can increase the transmission speed (and hence bandwidth) by a factor of 10 or more, so its distribution has a clear relation to cortical communication capacities, including synchronization capabilities. Several studies have reported volumetric abnormalities in white matter in autism, with enlargements in some areas and decreased volumes in other areas. The increased brain size in young children with autism is largely driven by white matter, particularly in the frontal lobes.[6,14]

The corpus callosum, which enables communication among specialized but collaborating functional systems in the two

hemispheres, is the most prominent white matter tract in the cortex. It is usually smaller in autism hence decreased corpus callosum size could be an index of white matter deficits that could contribute to impaired cortical connectivity. The abnormality of larger brain volume in autism has been found to be correlated with smaller corpus callosum size.[15] The abnormalities in white matter in autism suggest a plausible neural basis for disrupted systems-level connectivity in autism.

A number of early neurodevelopmental processes (such as neuronal migration and axonal pathfinding) could individually or in combination result in abnormalities in the brain's development of connectivity. Developmental alterations in axon number, axon pathfinding, synaptogenesis, and subsequent pruning of axons could result in abnormalities in the connectivity provided by white matter tracts.[16,17]

Disrupted Connectivity in Autism - The Under Connectivity Theory

The cortical underconnectivity theory states that inter-regional (systems level) connective circuitry in the brain is disrupted in autism and that patterns of thought that are particularly dependent on integration of frontal and more posterior contributions are disrupted. The theory proposes a causal link between the anatomical, physiological (brain activity), and psychological phenomena. Specifically, the theory states that the communication bandwidth among cortical areas, particularly between frontal and posterior areas, is lower in autism than in typical participants. Thus, any aspect of psychological or neurological function that is dependent on the coordination or integration of frontal brain regions with more posterior regions is susceptible to disruption, particularly when the task is complex and requires integration of different types of cortical computations.[18]

A PARTICULAR CASE OF GENETIC CONTRIBUTION TO AUTISM - DETAILS OF HOW AUTISM SPECTRUM SUSCEPTIBILITY GENE THOUSAND-AND-ONE AMINO ACID 2 KINASE (TAOK2) AFFECTS BASAL DENDRITE FORMATION IN NEOCORTEX

Researchers carried out a genome-wide association study of families from the autism genetic resource exchange, where they used two novel algorithms to search for recurrent copy-number variations in genotype data from 751 multiplex families with autism. They identified a novel, recurrent microdeletion and a reciprocal microduplication that carry substantial susceptibility to autism and appear to account for approximately 1% of cases.[19] Such regions of rare copy-number variation in families with autism were observed on chromosome 16. Both the deletion and the duplication are likely to be mediated by the 147-kb segmental duplication flanking the deleted or duplicated sequence.

The deleted or duplicated region on 16p11.2 contains 25 annotated genes or transcripts, and the flanking segmental duplications include an additional 3 genes. Thus, several of the genes contained in this region could be considered good candidates for driving the phenotype on the basis of their expression in the brain or function in neurodevelopment. TAOK2 is one such candidate gene. TAOK2, member of the mitogen-activated protein kinase (MAPK) kinase kinase family, the gene of which is located on the autism spectrum disorders (ASDs) susceptible region on chromosome 16p11.2, is essential for dendrite morphogenesis. They have described a new pathway that specifically affects the formation of basal dendrites and axonal projections in cortical pyramidal neurons. TAOK2 interacts with neuropilin 1 (Nrp1), a receptor protein that binds the secreted guidance cue semaphorin 3A (Sema3A), and they have delineated a pathway from these results whereby Sema3A and Nrp1 transduce signals through TAOK2 and c-Jun N-Terminal kinase (JNK) to regulate basal dendrite development in cortical neurons.[20]

The pyramidal neurons, which are abundant in brain regions associated with complex cognitive functions, including the cortex, hippocampus, and amygdale, have a dendritic tree that is divided into two domains: The apical dendrite, which extends toward the pial surface, and basal dendrites, which emerge from the base of the cell body. The majority of synapses received by neocortical pyramidal neurons form on the basal dendrites.[21] Evidence suggests that aberrant dendritic arborization of the pyramidal neurons might contribute to neurodevelopmental and psychiatric disorders with delayed onset, such as ASDs. In autistic children, dendritic branching of both CA4 and CA1 neurons was less than controls, and CA4 neurons were smaller in perikaryon area. These findings are consistent with previous studies and suggest a curtailment in maturation in the pathogenesis of autism.[22] However, little is known about the molecular pathways that control the formation of basal dendrites. Thus, the work done by de Anda et al. (2012)[20] sheds considerable amount of light to the understanding of the distinct physiology and morphology of these neurons whereby the mechanisms underlying sophisticated cognitive functions in normal and disease conditions can be elucidated.

TAOK1 and TAOK2 serine/threonine protein kinases are known to activate MAPK pathways (JNK, p38 or extracellular signal-regulated kinase), leading to the modulation of gene transcription. Binding of Nrp1 to Sema3A induced TAOK2 phosphorylation thereby activating TAOK2.

It has been discussed above how improper dendritic arborizations which might lead to autism. These matters are now further discussed in somewhat greater detail.

Distribution of TAOK2 and Activated (pTAOK2) in Neurons

Analysis of TAOK2 immunoreactivity in mouse cortical neurons dissociated at embryonic day (E) 17 and cultured 2 days in vitro showed that TAOK2 preferentially localized to growth cones. The growth cone is a region where actin specifically and exclusively accumulates and where the actin cytoskeleton is the most dynamic. In contrast, the activated pTAOK2 localized to the neurite shaft where microtubules also accumulate.[20]

Effects of Overexpression and Downregulation of TAOK2 in Basal Dendrite Formation and Axon Elongation

The initial experiments were done on cultured mouse cortical neurons using Taok2 shRNA and rTAOK2 constructs. TAOK2 shRNA or short hairpin RNA targeted different coding sequences of TAOK2 to acutely knock down its expression and rTAOK2 or resistant version of TAOK2 cDNA was used to rescue the TAOK2 shRNA phenotypes. Knockdown of TAOK2 resulted in impaired axon formation, decrease in the number of intact growth cones and their F-actin content per neuron. In addition, a decrease in the number of neurites and the number of secondary branches per cell was observed. Overexpression with the help of rTAOK2 increased the number of primary but not secondary neurites as compared with the controls.

To determine the effect of TAOK2 on post-migratory differentiation of cortical neurons *in vivo*, they used *in utero* electroporation techniques to insert the TAOK2 shRNA, control shRNA and rTAOK2 plasmids in E15 mouse embryos. Consistent with the previous findings, they found that downregulation of TAOK2 resulted in significantly fewer primary dendrites and less complex basal dendritic arborization than the controls, whereas TAOK2 overexpression significantly increased the complexity of dendritic arbor without affecting the apical dendrites.

TAOK2 shRNA-mediated downregulation also led to a decrease in the number of callosal axons traversing the midline which is also consistent with the facts stated by[23] regarding a smaller sized corpus callosum being found in the autistic patients which largely contribute to impaired cortical connectivity.

Interactions of Receptor Nrp1 and Secreted Guidance Cue Sema 3A with TAOK2

It was found that TAOK2 interacts with this pathway to modulate neuronal differentiation.[22] Co-immunoprecipitation tests, probing for interactions between TAOK2 and Nrp1 were positive. Selective co-localization of activated pTAOK2 with Nrp1/Sema and increased pTAOK2 immunoreactivity in Sema3A treated mouse cortical neuronal cultures further

enhanced the understanding of the interactions whereby the Sema3A bound to Nrp1 is capable of activating TAOK2.

Activated TAOK2 leads to stimulation of the JNK pathway. Phosphorylated JNK is required for the maintenance of neuronal microtubules in axons and dendritic architecture *in vivo*.[24,25] However, little is known about the molecular pathway that exclusively determines the formation of basal dendrites in pyramidal neurons. Experiments where overexpression of TAOK2 ameliorated the defective dendritic arborization in Nrp1^{Sema-} neurons confirmed the fact that TAOK2 acts downstream of Nrp1^{Sema3A}. The previous studies have shown that TAOK2 modulates activation of JNK by its dual phosphorylation at Thr183 and Tyr185.[26] Analysis of mouse cortical neuronal cultures showed that activated (phosphorylated) pJNK significantly localized in basal dendrites as compared to the apical dendrites. This compartmentalization of pJNK might be the reason for the preferential elongation of basal versus apical dendrites in neurons that have a fully functional Nrp1^{Sema3A} - TAOK2-JNK.

These observations, considered collectively, constitute evidence that Sema3A, TAOK2 and JNK act in the same pathway to modulate neuronal differentiation in cortical pyramidal neurons. They also indicate a molecular pathway whereby TAOK2 governs the morphogenesis of pyramidal neurons in the developing cortex.

DISCOVERY OF MIRROR NEURONS IN MONKEYS

Mirror neurons were originally discovered in the ventral premotor cortex (area F5) of the macaque monkey.[27] The defining characteristic of these neurons is that they discharge both when the monkey performs a motor act and when the monkey, at rest, observes another individual (a human being or another monkey) performing a similar motor act. For most mirror neurons, however, the relationship between the effective observed and executed motor acts is based on their common goal (e.g., grasping), regardless of how this goal is achieved (e.g., using a two-finger or a whole-hand technique). Mirror neurons have also been described in the prefrontal gyrus (PFG) and anterior intraparietal areas of the inferior parietal lobule (IPL). The parietal mirror neurons, similar to the premotor cortex mirror neurons code for the goals of motor acts rather than the movements from which they are constructed. The PFG and anterior intraparietal areas are both connected with the F5 area and the cortex of the superior temporal sulcus.[28]

MIRROR NEURONS IN HUMANS

Research using transcranial magnetic stimulation and functional magnetic resonance imaging (fMRI) has been interpreted by many researchers as evidence that humans also have mirror neurons or, more broadly, a "mirror neuron

system." In addition, a number of fMRI experiments have compared the cortical areas activated by execution of action without visual feedback, and passive observation of similar actions, and found that they overlap in regions broadly homologous with those where mirror neurons have been found in monkeys.[29,30] This evidence of mirror activation in humans has been augmented by studies indicating observation-execution overlap at the level of individual voxels in single subjects and cross-modal repetition suppression in two classical mirror areas: The inferior frontal gyrus (IFG)[31] and inferior parietal lobe. For example, blood oxygen level dependent (BOLD) responses to action observation were attenuated following execution of a similar, relative to dissimilar actions.

EXPERIMENTAL EVIDENCES SUPPORTING THE MIRROR NEURON HYPOTHESIS OF AUTISM

Mu-wave Suppression

Electroencephalography (EEG) has been a powerful tool useful tool in the investigation of the mirror neuron impairment in autism. The mu rhythm (an EEG rhythm recorded from the motor cortical areas) is a consequence of downstream modulation of motor neuron cells by the premotor cortex.[32] A possible link between the mu rhythm and "mirror neurons" was first suggested by Altschuler et al., (1997)[33] but it was Oberman et al. (2005)[34] who experimentally demonstrated that although individuals with ASD exhibited a suppression of mu rhythm during voluntary movements this suppression was absent when they observed someone else performing the same voluntary movement. The study also revealed that mu rhythm suppression depended on the familiarity of the observer with the agent and that individual with ASD showed mu wave suppression when a familiar person performed the action but not when it was performed by an unfamiliar person. These experimental data thus support the hypothesis that mirror neuron function is impaired in autism, in a manner that relates closely to imitation ability.

FMRI experiments have been significant in establishing the correlation between imitation and autism. Neural correlates of imitation in a group of normal IQ adolescent males with autism were examined[35] and marked differences in the parietal lobe and Broca's area were observed, and the contrast was more dramatic with the increase in complexity of the imitation task.[36] This study also shed light on the imitation versus observation impairment in autism, including differential activity in the amygdala across several conditions and also in a location within the posterior aspect of the superior temporal sulcus (pSTS) region. In controls, the pSTS region remained active during imitation but hardly active during observation whereas reverse was the case for individuals with ASD.[37] As pSTS provides visual input into the mirror neuron system, this study suggested that imitation

impairment in autism is associated with dysfunction of the mirror neuron system.

Structural and Functional Neuroimaging

The neural substrate for cognition and other mental state attribution, such as empathy, has now been well investigated and reviewed.[38] Cognition primarily involves three brain areas: The medial prefrontal cortex, pSTS, and the temporal lobe. Studies regarding empathy have also highlighted roles of anterior cingulate, temporal pole and[39,40] Gallese et al. (2004)[41] have argued that the insula is part of the mirror neuron system as it may also serve to match for "domain-specific" actions, and therefore, mirror neurons are important for empathy. Most strikingly decreased cortical thickness in the mirror neuron regions in both the parietal and ventral premotor cortex in individuals affected with ASD has been demonstrated by neuro cytoarchitectural studies.[42] Several studies have also been conducted on white matter connectivity in autism[43,44] raising the possibility that impaired mirror neuron function in autism could be explained by deficits in connectivity between elements of the network.[45] A close relationship between activities in Broca's area during observation and imitation of emotional expression and measures of empathic ability in children have been demonstrated recently as well.[46]

Electromyographic Studies

Deficits in the mirror mechanism in ASD have also been addressed from another perspective. The EMG activity of the mylohyoid Muscle has showed that observation of food grasping produced activation of the mylohyoid muscle in healthy individuals but not in ASD-affected individuals which imply that the observation of an action done by another individual intruded into the motor system of a typically developing observer was lacking in children with ASD. This finding indicates that, in this disorder, the mirror system is silent during action observation, and that the immediate, experiential understanding of the intentions of others is absent in ASD-affected individuals.[47]

IMPACT OF MIRROR NEURON DYSFUNCTION ON ASD

Improper Imitation Learning

Imitation learning is the means by which skilled movements are learned through the observation of others.[48] Imitation is informed by the principles of motor learning which describe the development of motor skills as being practice-dependent.[49] Error feedback is obtained from sensory functions, which require cross-modal translation before it can influence the motor-programing function. During imitation, observation of another individual's behavior may

serve as the sensory input against which to compare one's own motor plans. Motor learning and imitation are therefore intentional and incremental learning processes. Oztop et al. (2006)[50] have developed sophisticated computational models that show how mirror neurons may serve imitation. Williams et al. (2007)[51] investigated this process in an fMRI study of imitation where brain activity was compared between imitation and a condition where an alternative learnt action was enacted. Differences in parietal and dorsal premotor cortex reflected mirror neuron function, whereas differences in lateral orbitofrontal cortex (OFC) and caudal anterior cingulated cortex and lateral OFC is thought to serve behavioral change in response to error feedback. Consistent with this, A strong theoretical case has been made for abnormality of the amygdale - OFC circuit in autism.[52,53] Reduced influence of the amygdale-orbitofrontal circuit on the mirror neuron system could be important in influencing the socialization of action-learning in autism. This could be an important developmental influence and offers a feasible mechanism for developmental dysfunction of the mirror neuron system in autism.

Failure to Understanding of Goals and Intentions

A large number of studies based on noninvasive electrophysiological brain imaging studies showed that the observation of transitive actions done by others results in an increase in BOLD signal not only in visual areas but also in the IPL and the ventral premotor cortex, as well as the caudal part of the IFG. Both the premotor and the parietal areas of the human mirror system show a somatotopic organization. Observation of motor acts done with the leg, hand or mouth activates the precentral gyrus and the pars opercularis of the IFG in a medial-to-lateral direction. In the IPL, mouth motor acts are represented rostrally, hand and arm motor acts are represented caudally, and leg motor acts are represented even more caudally and dorsally, extending into the superior parietal lobule. Most studies on the mirror mechanism in humans have investigated transitive movements such as grasping. Recent fMRI studies have indicated that the human brain is endowed with a reaching mirror mechanism that is anatomically distinct from the mirror mechanism that codes for the distal motor act. fMRI study based on "repetition suppression" technique that the trial-by-trial graded reduction of a physiological response to repeated stimuli). The results showed that repeated presentation of the same goal caused suppression of the hemodynamic response in the left intraparietal sulcus complementing the parieto-frontal mirror network.

The significance of the mirror system in understanding the intentions of others was demonstrated by "mental state inference" model[50] in which a simulation mechanism was implemented to obtain a motor code compatible with the observed action in which a candidate (motor code Y) is able to mentally simulate its execution and the sensory feedback

that would be perceived along with a series of virtual sensory signals (designated as Simg) which could be analytically compared with the actual signals (Sactor) which could possibly yield an error for the motor code Y.

Misguided Development of Egocentrism and Allocentrism

It has often been suggested that ASD-affected individuals are extremely "egocentric"[54,55] had challenged this view, arguing that people with autism are in fact the exact opposite - extreme allocentrists. Undirected intelligence reflects a lack of "egocentricity," characterized by failure to encode experience in terms of its personal relevance. Developmentally, a deficit in mirror neuron function in autism could result in a failure to discriminate (in terms of learning different patterns of responses) between self-directed and other actions, resulting in a tendency to treat all behavioral observations similarly, regardless of whether they are directed at one's self or not. This may give rise to an apparent lack of interest in other people's behavior and attitudes.

Wrongful Associative Learning

Associative learning, also referred to as "Hebbian learning" is a form of learning that results from exposure to a relationship between two events. Research examining the effects of conditioning procedures on animal behavior has shown that associative learning depends on "contiguity" - the closer the two events occur in time, the stronger the association - and "contingency" - there needs to be a correlation or predictive relationship between them. Both psychological and neural models[56] of associative learning suggest that the change in behavior results primarily from the strengthening of existing connections between event representations. In the neural case, this implies the facilitation of synaptic transmission involving the mirror neuron networks.

CONCLUSION

Several studies have indicated the actions of various molecules in dendrite arborization. However, the molecular differences that may direct the formation of different domains within the same dendritic tree remain almost unknown. A part of this review was dedicated to the consideration of a TAOK2 mediated mew molecular pathway that preferentially modulates the formation of basal dendrites in cortical pyramidal neurons. This review supports the hypothesis that underdeveloped neuron morphology contributes to the disconnection of brain regions that may underlie the autistic phenomena. The discovery of mirror neurons has had a profound effect on the field of social cognition. Here, we have reviewed what is currently known about mirror neurons in the different cortical areas in which they have been described. Experimental studies have now established that mirror neurons, and counter-mirror neurons, contribute

to a variety of social cognitive functions, including action understanding, action prediction, imitation, language processing and mentalizing. There is also now growing evidence that the functional role(s) of mirror neurons and whether mirror neurons arise as a result of a functional adaptation and/or of associative learning during development are important questions that still remain to be solved and very little empirical work has been conducted in investigating these effects. The challenge will be to excavate the molecular players regulating mirror neuronal milieu in the complex cognitive systems supporting human sociality.

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