



# Brain plasticity in paediatric neurology

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Plasticity includes the brain's capacity to be shaped or moulded by experience, the capacity to learn and remember, and the ability to reorganize and recover after injury. Mechanisms for plasticity include activity-dependent refinement of neuronal connections and synaptic plasticity as a substrate for learning and memory. The molecular mechanisms for these processes utilize signalling cascades that relay messages from synaptic receptors to the nucleus and the cytoskeleton to control the structure of axons and dendrites. Several paediatric neurological disorders such as neurofibromatosis-1, Fragile X syndrome, Rett syndrome, and other syndromic and non-specific forms of mental retardation involve lesions in these signalling pathways. Acquired disorders such as hypoxic-ischaemic encephalopathy, lead poisoning and epilepsy also involve signalling pathways including excitatory glutamate receptors. Information about these 'plasticity pathways' is useful for understanding their pathophysiology and potential therapy.

*Keywords:* Plasticity. Glutamate. Mental retardation. Neurofibromatosis. Fragile X syndrome. Rett syndrome.

## Introduction

Plasticity, derived from the Greek word *plaitikos*, 'to form', has taken on several special connotations in neurology, including the brain's capacity to be shaped or moulded by experience, the capacity to learn and remember, and the ability to reorganize and recover after injury.<sup>1–3</sup> Plasticity is an important concept in paediatric neurology, which deals with infants and children whose brains are more flexible and resilient than those of adults. Children appear to have greater capacity for learning and memory than adults and their capacity to recover from injuries or radical surgical treatments such as hemispherectomy is greater. Progress in neuroscience is providing some insights into the molecular signalling pathways that mediate neuronal plasticity, and this review highlights some ways in which this information is relevant to understanding neurological disorders of children.

## Adaptive plasticity

Adaptive plasticity is used here to refer to reorganization of brain circuits that promotes improved or adaptive functioning in response to a change in sensory stimulation or injury. For example, functional brain imaging has illustrated remarkable changes in brain circuitry associated with prolonged practice from early childhood in musicians who play stringed instruments, deprivation of visual stimulation by congenital blindness, or recovery of speech after removal of eloquent cortex in children with epilepsy. In the case of the string players, Elbert *et al.*<sup>4</sup> used magnetic source imaging to demonstrate that the cortical representation of the left hand, which fingers the strings, was increased in direct proportion to how early in childhood they began to practice. This suggests that a longer continuous period of activity in the left hand caused more reassignment of cortex than

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playing that began later in life. In people who had never experienced vision because of a congenital ocular abnormality, Sadato *et al.* used positron emission tomography (PET) for glucose to demonstrate that they activated visual cortex when they touched Braille letters with the index finger of their left hand.<sup>5</sup> This suggested that activation of somatosensory cortex used to read Braille had become linked to activation of the occipital visual cortex which had never been stimulated by visual input. Hertz-Pannier *et al.* used functional magnetic resonance imaging (fMRI) to study plasticity for language after left hemispherectomy for Rasmussen's encephalitis produced profound aphasia and alexia in a 9-year-old child.<sup>6</sup> Postoperative fMRI at age 10 years 6 months showed a shift of language-related networks to the right hemisphere during expressive and receptive tasks associated with recovery of language skills. This is consistent with the study by Boatman *et al.* which documented language recovery in a series of children with late onset seizures who underwent hemispherectomy.<sup>7</sup> These examples demonstrate rearrangement of neuronal circuits in cerebral cortex associated with functional plasticity that enhances or restores functional ability.

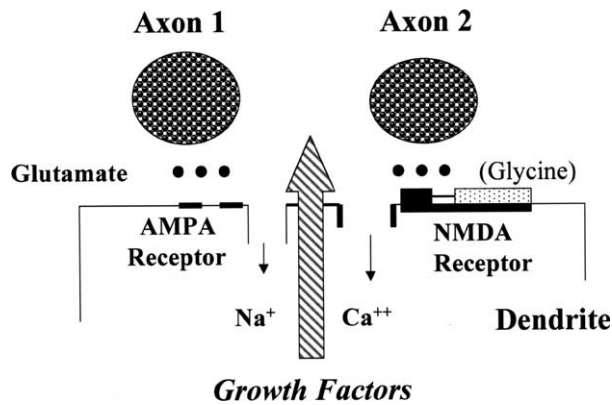
### ***Plasticity and refinement of synaptic connections***

Although several potential cellular mechanisms for brain plasticity have been identified, including death by apoptosis, or programmed cell death,<sup>8</sup> and birth of new neurons,<sup>9</sup> it seems likely that the primary mechanism underlying the kinds of plasticity demonstrated by these functional imaging studies reflects reorganization of synapses.<sup>1</sup> Synaptic activity, especially excitatory activity generated by the release of the neurotransmitter glutamate, and activation of glutamate receptor-channel complexes, appears to be the most important basis for signals generated by functional imaging.<sup>10</sup> In the case of glucose-PET, the primary site of glucose uptake in the brain is in areas enriched in neuropil containing synaptic connections.<sup>11,12</sup> There is a strong correlation between release of glutamate and anaerobic consumption of glucose by glutamate transporters on peri-synaptic glia. Histological analyses of cerebral cortex from animals in which somatosensory inputs have been experimentally ablated have also demonstrated rearrangements of axonodendritic connections.<sup>1,13</sup>

The immature brain is more adept at reorganizing its synaptic connections than the adult brain, and an important reason for this advantage may be the greater number of synaptic connections in the developing brain compared with the adult.<sup>3,14,15</sup> Studies in which synapses have been counted in postmortem human specimens indicate that cortical synaptic density increases approximately twofold from birth to 2 years of age, followed by a reduction in density by the early teenage years.<sup>13</sup> Glucose-PET studies show a similar developmental curve, reflecting the strong link between synaptic activity and glucose consumption mentioned above.<sup>16</sup> From the age of 2 years until early adulthood, plastic reorganization of synaptic connections occurs through a process of activity-dependent refinement or pruning of a surplus of synaptic connections, and this is the period when plasticity is enhanced. For example, the critical period for ocular dominance plasticity in humans ends at about age 10 years, when synapse density in the occipital cortex begins to decline steeply.<sup>17</sup> The ability of the developing brain to choose to stabilize certain synapses and to prune or 'sculpt' the others probably contributes to its superior plasticity.<sup>3</sup>

### ***Plasticity depends on excitement***

Developing neuronal connections are shaped by the balance of excitatory and inhibitory pathways entering the brain from primary sensory modalities such as vision, hearing and somatosensory sensation as well as by the activity of intrinsic circuits.<sup>18</sup> Most of these pathways use glutamate as their neurotransmitter, and active pathways are likely to gain influence compared with quieter ones according to their pattern of activation of glutamate receptors.<sup>18,19</sup> Both NMDA (*N*-methyl-D-aspartate) and AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionate)-type glutamate receptor activation is involved in synapse formation and stabilization (Fig. 1). The NMDA-type glutamate receptor has received special attention because of its ability to detect when two or more pre-synaptic axons are active at the same time, and this allows them to be stabilized and preserved in a permanent circuit.<sup>19</sup> Stimulation of AMPA and NMDA glutamate receptors induces active remodelling of pre- and postsynaptic actin at synaptic sites. Activation of NMDA channels allows calcium to flux into neurons, activating protein kinases such as CaMKinase II and IV and production of neurotrophins such as BDNF.<sup>20,21</sup>



**Fig. 1.** Model of activity-dependent stabilization of synaptic connections at excitatory synapses. The *N*-methyl-D-aspartate (NMDA) type glutamate receptor channel complex on the right opens when it is occupied by both glutamate and glycine provided that the surrounding neuronal membrane is depolarized through stimulation of AMPA type glutamate receptors. This allows the NMDA receptor to detect synchronized firing of two axons (Axons 1 and 2 in the diagram). When the NMDA receptor opens, calcium fluxed through its channel stimulates the synthesis of neuronal growth factors, such as brain derived neuronal growth factor (BDNF), which supports the maintenance of both axons in a stable neuronal circuit.

Neurotrophins serve as retrograde signals for stabilizing synaptic connections, providing a mechanism by which synchronized, coincident excitatory activity in several axons can lead to activity dependent maintenance and refinement of those connections.<sup>19</sup> Axons that do not elicit growth factors from their targets whither away (Fig. 1).

## Learning and memory are based on synaptic plasticity

Learning and memory involve short-term changes in strength or efficacy of neurotransmission at synapses and longer-term changes in the structure and number of synapses.<sup>22</sup> The experimental models known as long-term potentiation (LTP) and long-term depression (LTD) demonstrate physiological increases or decreases in synaptic strength or effectiveness in response to repeated intense electrical stimulation that are believed to provide a physical and biochemical substrate for memory.<sup>23</sup> Stimulation of NMDA receptors is important for LTP, and the increased calcium entering through the NMDA channel leads to phosphorylation of AMPA receptors and insertion of more AMPA receptors into the postsynaptic membrane.<sup>24</sup> The

increase in the number and activity of AMPA receptors induced by NMDA receptor stimulation is thought to be responsible for the enhanced excitatory response when the synapse is stimulated at a later time. LTP is enhanced in the immature brain compared with the adult, and the enhanced activity of the NMDA receptor channel complex at this age is thought to be responsible.<sup>25,26</sup>

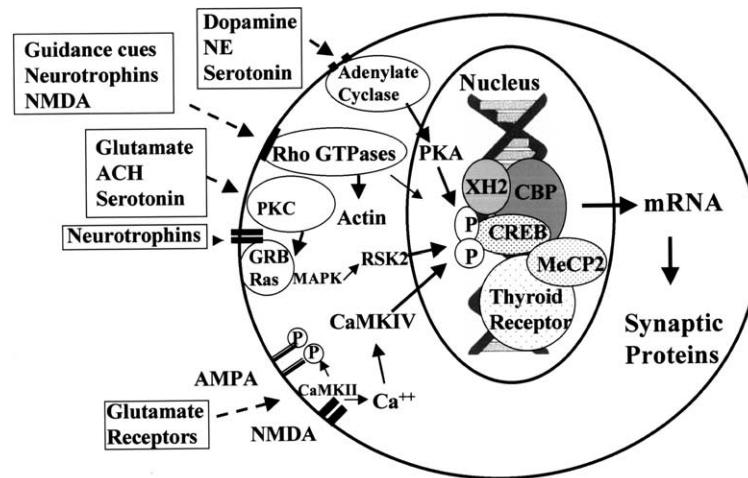
The fundamental mechanisms for synaptic plasticity involved in learning and memory appear to lie on a continuum with the mechanisms utilized for activity-dependent synaptic refinement and stabilization of neuronal circuits.<sup>19,27</sup> Both types of processes involve stimulation of neurotransmitters and other cell surface receptors, activation of intracellular signalling cascades and gene transcription, and synthesis of new proteins that change the physical shape and number of synapses<sup>3,28</sup> (Fig. 2). The brain appears to use a similar cascade of biochemical synaptic and intraneuronal events for shaping and refining large-scale changes in neuronal circuits in the immature brain as for more subtle changes involved in memory formation in adults. A major age-related difference may be that the surplus of synaptic connections present during early critical periods allows changes to occur at the level of axonal and dendritic branching, while in older individuals changes are restricted to more localized formation and activity-dependent rearrangement of synaptic spines.<sup>29</sup>

## Disorders that impair plasticity

Disorders that disrupt the mechanisms involved in neuronal plasticity are common in children, especially in those with cognitive impairment.<sup>3</sup> Genetic disorders such as neurofibromatosis type 1 and fragile-X syndrome as well as less common ones such as Coffin-Lowry, Rubinstein-Taybi, and Rett syndromes are all caused by mutations in signalling pathways that mediate activity-dependent neuronal plasticity (Table 1). Acquired disorders such as cretinism and lead poisoning also cause neurodevelopmental disabilities by disrupting these same pathways. A broad group of diverse paediatric neurological conditions are related to each other because they disrupt the pathways that mediate plasticity.

## Transcription disorders

Gene transcription is the final common pathway for encoding long-term memories and constructing



**Fig. 2.** Scheme of signalling pathways involved in learning, memory and neuronal plasticity as described in the text. Long-term memories and plasticity in neuronal circuits require transcription of new proteins and activation of the actin cytoskeleton that change synaptic connections. Multiple transcription factors respond to signalling from the plasma membrane, including the nuclear thyroid receptor, the transcriptional repressor MeCP2, the transcriptional activator CREB and co-activator CBP and the helicase XH2. Neurotransmitters, neurotrophins and other signals such as integrins activate signalling cascades that stimulate transcription through phosphorylation of transcription factors. Stimulation of NMDA receptors can produce long-term potentiation (LTP) through phosphorylation of AMPA receptors and phosphorylation of CREB. Abbreviations: Rho GTPases: Rho family of guanosine triphosphate binding protein switches; PKC: protein kinase C; PKA: protein kinase A; GRB: growth factor receptor adapter protein; Ras: another family of GTP binding proteins; MAPK: mitogen activated protein kinase/extracellular signal-regulated protein kinase; RSK2: ribosomal S6 kinase-2; CaMKIV: calcium calmodulin protein kinase IV; NMDA: *N*-methyl-D-aspartate; AMPA:  $\alpha$ -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid.

immature neuronal circuits in the developing brain, and disorders that disrupt transcription cause severe neurological disabilities<sup>22,27,28</sup> (Fig. 2). Early deficiency of thyroid hormone causes severe neurological disability associated with cretinism because the nuclear thyroid receptor represses transcription of many genes if it is not occupied by thyroxine.<sup>30</sup> The nuclear transcription factor MeCP2 is also a transcriptional repressor, and genetic defects in this protein cause Rett syndrome, which includes severe neurological disability as well as poor

somatic growth and autonomic abnormalities.<sup>31</sup> In this case, the brain develops relatively normally during fetal life without normal MeCP2 function, but the postnatal spurt in brain growth is impaired, suggesting that repression of certain genes is required for this phase.<sup>32</sup> CREB (cyclic AMP response element binding protein transcription factor) is required for learning and memory in fruit-flies, snails and mice, and it is normally activated by phosphorylation in response to signals from the cell surface via the Ras-MAPK (mitogen activated protein kinase) signalling cascade<sup>22,28</sup> (Fig. 2). Mutations in the protein kinase RSK2 that phosphorylates CREB cause the X-linked mental retardation syndrome Coffin-Lowry syndrome<sup>33</sup>, in which cognitive impairment in CLS correlates with reduced capacity for RSK2 activation in lymphoblasts from patients.<sup>34</sup> Rubinstein-Taybi syndrome, another form of mental retardation associated with dysmorphic features, is caused by mutations in CREB binding protein (CBP), a transcription factor that is a transcriptional co-activator with histone acetylase activity.<sup>35</sup> Nuclear depletion of nuclear CBP has also recently been implicated in the pathogenesis of Huntington disease, due to sequestration by aggregates of mutated Huntingtin protein.<sup>36</sup> X-linked mental retardation associated

**Table 1.** Disorders of plasticity and signalling pathways

Fragile X syndrome
Neurofibromatosis-1
Rett syndrome
Coffin-Lowry syndrome
Rubinstein-Taybi syndrome
Cretinism
Lead poisoning
Huntington disease
X-linked mental retardation with $\alpha$ -thalassaemia
Tuberous sclerosis-2
Aarskog (faciogenital dysplasia) syndrome
Non-specific mental retardation mutations in:
PAK3, oligophrenin 1,
Tetraspanin TM4SF2

with  $\alpha$ -thalassaemia (ATR-X syndrome), which includes short stature and dysmorphic features, is caused by mutations in the XH2 helicase that unwinds DNA to allow transcription.<sup>37</sup> Transcriptional disorders disrupt brain plasticity and development of somatic tissues because of the central role that gene expression plays in growth and development throughout the body.

## Disorders of signalling from the synaptic membrane

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Several types of mental retardation and milder cognitive disorders have been linked to defects in molecules that connect cell surface receptors to the actin cytoskeleton and downstream pathways that influence nuclear transcription.<sup>38</sup> Many of these disorders involve mutations in GTPases (guanosine triphosphate binding proteins), which are simple molecular switches that lie beneath the cell membrane and control complex cellular processes by switching between an active (GTP) and inactive (GDP) bound form.<sup>39</sup> One example is neurofibromatosis-1 (NF-1), a relatively common genetic cause for learning disorders that is caused by mutations in the neurofibromin protein. Neurofibromin functions in part as a regulator for GTPases as a so-called GTPase-activating protein (GAP).<sup>40</sup> A loss of function mutation in GAP is expected to disinhibit the GTPase switch and this has been detected in a mouse model of NF-1.<sup>39</sup> In the mouse, the activity of a type of GTPase called Ras is increased, and this is associated with an increase in  $\gamma$ -aminobutyric acid mediated inhibition and deficits in long-term potentiation and learning<sup>41</sup> (Fig. 2). These deficits can be reversed by genetic and pharmacological manipulations to decrease Ras. Tuberous sclerosis-2 is also related to mutations in a GAP protein.<sup>42</sup> Both the susceptibility to tumours and learning problems in these neurocutaneous disorders may be caused by too much 'noise' in GTPase signalling pathways.

Another family of GTPase proteins known as Rho GTPases is of interest because of their role in controlling the actin cytoskeleton, cell adhesion and migration and gene expression.<sup>43</sup> The actin cytoskeleton influences neuronal plasticity by controlling the size and shape of dendritic spines. Ramakers recently reviewed the relationship abnormalities in Rho proteins and mental retardation.<sup>44</sup> Several genes responsible for non-syndromic mental retardation, including oligophrenin-1 and PAK3 (p21-activated kinase 3), are related to Rho-GTPase signalling. Oligophrenin 1

acts as a Rho-GAP protein, similar in function to neurofibromin.<sup>45</sup> Mutations in a guanine nucleotide exchange factor (GEF) that activates the Rho GTPase Cdc42 is responsible for mental retardation in Aarskog syndrome or faciogenital dysplasia.<sup>46</sup> Mental retardation is also associated with X-linked mutations in the gene for the transmembrane protein TM4SF2, which impair the ability of integrins to activate the actin cytoskeleton.<sup>47</sup> Rho GTPases regulate integrin-mediated signals from the extracellular matrix to the actin cytoskeleton.

## Fragile X syndrome

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Recent progress based on the FMR1 gene knockout mouse suggests that this common form of mental retardation is also related to a defect in synaptic plasticity. The defective gene product, the FMRP protein, normally binds to a subset of messenger RNA and acts as a regulator of proteins translation.<sup>48</sup> Dendritic spines on apical dendrites of cortical pyramidal neurons of knockout mice have been shown to be longer, thinner and more tortuous than in wild type, and parallel pathological changes in humans with the disorder.<sup>49</sup> Huber *et al.* reported that synaptic long-term depression (LTD) in response to stimulation of metabotropic glutamate receptors is enhanced in these mice, and they suggest that this change is related to a reduction in synaptic AMPA receptors.<sup>50</sup> Li *et al.* found that the number of AMPA receptors as well as LTP was reduced in cerebral cortical synapses but not in other brain regions.<sup>51</sup> Reduced numbers of AMPA receptors would be expected to impair learning and memory as well as disrupting the formation and remodelling of dendritic spines. These results suggest the potential that the cognitive disorder of Fragile-X syndrome could be treated by manipulating the trafficking of AMPA receptors.

## Lead poisoning

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Lead continues to be a worldwide problem for young children who are exposed to the toxin in dust and in gasoline in some countries. Exposure to lead at the age of 2–3 years causes dose-related impairments in cognition that are persistent, but exposure during adulthood is far less harmful, suggesting that lead disrupts developing neuronal circuits.<sup>52</sup> In animal models there is evidence that lead can disrupt several steps involved in neuronal plasticity at the level of synaptic release of neurotransmitter, at the NMDA receptor and with protein

kinase (PKC). Lead binds to calcium sites on the synaptic vesicular protein synaptotagmin I, possibly impairing its interaction with other vesicular proteins.<sup>53</sup> Release of glutamate and GABA is impaired in the hippocampus by low level lead.<sup>54</sup>

Lead has also been reported to block NMDA receptors, impair LTP and reduce CREB phosphorylation in the developing brain.<sup>55,56</sup> Low level lead also activates intracellular PKC and elevates the induction of the transcription factor zif268 in the hippocampus in response to electroshock.<sup>57</sup> It is noteworthy that stimulation of PKC can increase signalling through the Ras-MAPK pathway to RSK2, as discussed above.<sup>28</sup> With respect to its effect on PKC, lead may have an effect on signalling similar to the lesion in NF-1, which increases the background level of Ras signalling. On the other hand, effects on vesicular proteins and NMDA receptors may impair signalling through the synapse. Taken together, these findings suggest that lead may impair the 'signal to noise' relationship in developing synapses. Studies using an immature animal model suggest that lead impairs neuronal growth and activity-dependent refinement of synaptic connections in the developing brain.<sup>58,59</sup> Guilarte *et al.* also recently reported that in developing rodents, environmental enrichment can reverse cognitive and molecular deficits induced by developmental lead exposure.<sup>60</sup>

## Epilepsy

Children are far more prone to seizures than the adults, and work in animal models suggests that this is due to the imbalance of excitatory over inhibitory circuits associated with enhanced plasticity in the immature brain.<sup>61</sup> As described above, the hippocampus is enriched in excitatory neuronal circuits because of its role in learning and memory, and injury to these circuits followed by plastic reorganization has been proposed to cause partial complex seizures associated with mesial temporal sclerosis.<sup>62</sup> In adult animal models of repeated seizures or status epilepticus, neuronal death in the dentate gyrus and CA3 of the hippocampus is associated with enhanced neurogenesis of dentate granule neurons and sprouting of mossy fibres projecting from granule cells.<sup>63</sup> Chronic seizures are thought to result from aberrant synapses between these sprouting mossy fibres and adjacent granule cells or CA3 pyramidal neurons.<sup>62,63</sup> Although immature dentate granule neurons are less vulnerable to status epilepticus than those in adult rodents, enhanced neurogenesis in the dentate

gyrus causes a similar phenomenon.<sup>61</sup> These changes are associated with deficits on cognitive and motor testing, which have been reported to be reversible if the animals are provided with a stimulating 'enriched' environment.<sup>64</sup> Studies of hippocampal tissue removed from patients undergoing epilepsy surgery have also demonstrated neuronal loss and aberrant mossy fibre sprouting as well as increases in biochemical markers for AMPA and NMDA glutamate receptors and decreases in GABA receptors.<sup>65-70</sup> These changes may contribute to neuronal hyperexcitability and seizure generation.

## Neonatal hypoxic ischaemia

Disrupted plasticity also plays a role in other acquired disorders, such as brain injuries from perinatal hypoxia-ischaemia.<sup>71</sup> In these disorders, the developing brain's capacity for plasticity can become its 'Achilles' heel' as molecular mechanisms required for excitatory neurotransmission become accidentally over-stimulated to cause injury in the face of energy failure.<sup>72</sup> In the fetus or premature infant, expression of non-NMDA type glutamate receptors on immature oligodendroglia, during a critical window in development, makes them vulnerable to glutamate-mediated cell death leading to periventricular leukomalacia.<sup>73</sup> Later in gestation, the enhanced function of immature NMDA receptors contributes to the selective vulnerability of neuronal circuits in the thalamus, basal ganglia and cerebral cortex to near-total asphyxia.<sup>71</sup> After this type of injury, neuronal imbalances and plastic reorganization in the basal ganglia probably contribute to the emergence of rigidity and dyskinesias in extrapyramidal cerebral palsy.<sup>74</sup> Enhanced plasticity mechanisms in the immature brain contribute both to special patterns of pathological vulnerability to injury from hypoxic ischaemia as well as to reorganization that leads to delayed evolution of abnormalities in tone and movement.

## Conclusion

The signalling pathways that shape developing neuronal circuits during childhood and continue to subserve learning and memory throughout life appear to be highly conserved across species from fruit flies to humans. An enlarging group of genetic paediatric disorders that affect these pathways are being identified. In addition, these pathways

are involved in the pathogenesis of injury and recovery from acquired disorders such as hypoxic-ischaemic encephalopathy, epilepsy and lead poisoning. Information about these 'plasticity pathways' is useful for understanding the pathophysiology of many neurological disorders in children and should also help to advance therapy.

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