REVIEW

Urokinase-type plasminogen activator is a modulator of synaptic plasticity in the central nervous system: implications for neurorepair in the ischemic brain

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Abstract

The last two decades have witnessed a rapid decrease in mortality due to acute cerebral ischemia that paradoxically has led to a rapid increase in the number of patients that survive an acute ischemic stroke with various degrees of disability. Unfortunately, the lack of an effective therapeutic strategy to promote neurological recovery among stroke survivors has led to a rapidly growing population of disabled patients. Thus, understanding the mechanisms of neurorepair in the ischemic brain is a priority with wide scientific, social and economic implications. Cerebral ischemia has a harmful effect on synaptic structure associated with the development of functional impairment. In agreement with these observations, experimental evidence indicates that synaptic repair underlies the recovery of neurological function following an ischemic stroke. Furthermore, it has become evident that synaptic plasticity is crucial not only during development and learning, but also for synaptic repair after an ischemic insult. The plasminogen activating system is assembled by a cascade of enzymes and their inhibitors initially thought to be solely involved in the generation of plasmin. However, recent work has shown that in the brain this system has an important function regulating the development of synaptic plasticity via mechanisms that not always require plasmin generation. Urokinase-type plasminogen activator (uPA) is a serine proteinase and one of the plasminogen activators, that upon binding to its receptor (uPAR) not only catalyzes the conversion of plasminogen into plasmin on the cell surface, but also activates cell signaling pathways that promote cell migration, proliferation and survival. The role of uPA is the brain is not fully understood. However, it has been reported while uPA and uPAR are abundantly found in the developing central nervous system, in the mature brain their expression is restricted to a limited group of cells. Remarkably, following an ischemic injury to the mature brain the expression of uPA and uPAR increases to levels comparable to those observed during development. More specifically, neurons release uPA during the recovery phase from an ischemic injury, and astrocytes, axonal boutons and dendritic spines recruit uPAR to their plasma membrane. Here we will review recent evidence indicating that binding of uPA to uPAR promotes the repair of synapses damaged by an ischemic injury, with the resultant recovery of neurological function. Furthermore, we will discuss data indicating that treatment with recombinant uPA is a potential therapeutic strategy to promote neurological recovery among ischemic stroke survivors.

Key Words: *cerebral ischemia; neurorepair; plasminogen; plasticity; stoke; synapse; urokinase; urokinase receptor*

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Introduction

The importance of synaptic plasticity in the process of neurorepair in the ischemic brain has been recognized by a large number of investigators that have focused their work on neurogenesis, reorganization of cortical representation (Font et al., 2010), and plasticity-related structural, biochemical and functional changes in the synapse after an ischemic injury (Murphy and Corbett, 2009). This process has significant translational relevance because cerebral ischemia has a rapid and dramatic effect on synaptic structure and function (Hofmeijer and van Putten, 2012) associated with the development of irreversible neurological deficits (Hasbani et al., 2016). In line with these observations, synaptic repair is associated with the recovery of neurological function following an ischemic injury (Diaz et al., 2017). We have performed a PubMed literature search of articles in the period of January 1968–August 2019 on "urokinase-type plasminogen activator", "synaptic plasticity" and "neurorepair". Here we will use this conceptual frame to review experimental evidence indicating that urokinase-type plasminogen activator (uPA) plays a central role in the process of synaptic repair in the ischemic brain, and to discuss the clinical implications that these findings have for the treatment of acute ischemic stroke survivors.

The Plasminogen Activating System

Plasminogen activators (PAs) are serine proteases that by cleaving a specific Arg-Val peptide bond of the proenzyme plasminogen catalyze its conversion to the broad-spectrum protease plasmin (Pittman et al., 1989). Tissue-type plasminogen activator (tPA) and uPA are two PA's found in mammalian tissue, where they mediate several biological processes such as fibrinolysis, inflammation, angiogenesis, and tissue remodeling (Saksela, 1985; Saksela and Rifkin, 1988; Seeds et al., 1999). Significantly, recent *in vitro* and *in vivo* work indicates that tPA and uPA are also found in the synapse, where they play a plethora of roles that not always require plasmin generation (Echeverry et al., 2010, 2012; Jeanneret et al., 2016, 2018; Diaz et al., 2017, 2018; Merino et al., 2017, 2018). More specifically, it has been shown that in cerebral cortical neurons

tPA is stored in presynaptic vesicles (Wu et al., 2015), and that its rapid release following the onset of cerebral ischemia activates cell signaling pathways that protect the structural and functional integrity of the synapse from the harmful effects of the acute ischemic injury (Wu et al., 2012, 2013; Jeanneret et al., 2018). Furthermore, it has been shown that tPA plays a central role on neuronal migration (Seeds et al., 1999). Likewise, recent studies indicate that in contrast with the release of tPA during the acute stages of the ischemic insult, cerebral cortical neurons release uPA during the recovery phase of cerebral ischemia (Wu et al., 2014), and that binding of this protease to its receptor (uPAR) plays a central role in the process of synaptic repair in neurons that have survived an ischemic lesion.

The Urokinase-Type Plasminogen Activator/ Urokinase-Type Plasminogen Activator Receptor System

uPA is a serine proteinase assembled by an amino-terminal domain that binds to uPAR, a kringle domain that interacts with plasminogen-activator inhibitor-1 (PAI-1; uPA's inhibitor) (Lawrence et al., 1989), and a catalytic carboxylic-terminal with the protease domain. Single chain uPA is known as pro-uPA because for a long time it was believed not to have peptidase activity (Wun et al., 1982). However, soon after its characterization it was found that pro-uPA is not inactive, and instead that it can cleave plasminogen into plasmin, which in turn converts pro-uPA into a two-chain form by cleaving its Lys158-Ile159 bond (Stepanova and Tkachuk, 2002). Importantly, two-chain uPA cleaves plasminogen into plasmin at a rate 200-fold higher than pro-uPA (Lijnen et al., 1989). In the brain uPA expression is developmentally regulated. Accordingly, while uPA is found in large numbers of projections neurons and oligodendrocytes during early stages of development (Dent et al., 1993), in the adult brain its expression is limited to well circumscribed groups of neurons in the hippocampus, and in some subcortical structures (Vassalli et al., 1991; Sappino et al., 1993), namely the entorhinal and parietal cortex and the subcolicular complex (Masos and Miskin, 1996).

uPAR is a glycosylphosphatidylinositol (GPI)-anchored protein assembled by three domains, D1, D2 and D3, with high affinity for uPA, pro-uPA, and uPA's amino terminal factor (ATF, assembled by uPA's first two domains). Due to its GPI-anchorage, uPAR has high motility on the plasma membrane, and forms clusters in the caveolae of the leading edge of migrating cells (Andreasen et al., 1997). The expression of uPAR in neurons also varies with the developmental stage. Thus, while at *in vitro* day 3 it is found in all neurites, in mature cultured neurons its expression is limited to few dendritic and axonal growth cones. In contrast, the *in vivo* expression of uPAR in the developing and mature brain under physiological conditions has not been fully characterized yet.

In contrast with these observations, following mechanical trauma *in vitro* and cerebral ischemia *in vivo*, uPA and uPAR expression returns to levels comparable to those seen in early developmental stages *in vitro* (Wu et al., 2014; Merino et al., 2017). Importantly, experimental evidence indicating that hypoxia-inducible factor-1 (HIF-1α) regulates the expression of uPA and uPAR (Krishnamachary et al., 2003; Nishi et al., 2016) suggests that HIF-1α is the mediator of the observed increase in their abundance in the ischemic brain. Furthermore, it has also been described that the expression of uPA and uPAR increases in microglia in response to inflammatory stimuli such us the injection of lipopolysaccharide or prion disease inoculation (Cunningham et al., 2009). However, in contrast with our observations in the ischemic brain, it is unclear if HIF-1α also mediates the increase in uPA and uPAR in microglia following these stimuli.

As described above, uPA binding to uPAR regulates the activity of the plasminogen activating system on the cell surface by a sequence of events that begin with the binding of pro-uPA and uPA to uPAR, which in turn are followed by uPA-catalyzed conversion of plasminogen into plasmin, and plasmin-induced cleavage and activation of pro-uPA (Smith and Marshall, 2010). Notably, pro-uPA bound to uPAR is activated by plasmin more efficiently than unbound uPA (Ellis et al., 1989). Due to its lack of a transmembrane and cytoplasmic domains, to transduce signals across the plasma membrane uPAR needs co-receptors, such as the low-density lipoprotein receptor-related protein-1 (LRP1) (Herz and Strickland, 2001), α3β1, α5β1, αVβ5, αVβ3, and αVβ2 integrins, ENDO180, platelet-derived growth factor receptor-β, and epidermal growth factor receptor (Smith and Marshall, 2010). Importantly, PAI-1 is one of the main inhibitors of uPA, and the uPA-uPAR-PAI-1 complex is internalized by LRP-1 in clathrin-coated pits. In the endosomes, uPA and PAI-1 dissociate from LRP-1 and are degraded by lysosomes, while uPAR and LRP-1 are recycled back to the membrane (Nykjaer et al., 1997). Besides regulating plasmin generation on the cell surface, uPA binding to uPAR also activates cells signaling pathways including the Tyr kinases focal adhesion kinase and Src, the Ras-mitogen-activated protein kinase, and the Rho family of small GTPases (Blasi and Carmeliet, 2002).

Urokinase-Type Plasminogen Activator and Urokinase-Type Plasminogen Activator Receptor Induce Synaptic Plasticity in the Ischemic Brain

The tripartite synapse

The concept of "tripartite synapse" describing the functional interaction between perisynaptic astrocytes, the extracellular matrix and the axonal bouton and opposing dendritic spine (Perea et al., 2009), conceptualizes the fact that astrocytes regulate synaptic function. Accordingly, astrocytes promote structural plasticity (Bernardinelli et al., 2014), and induce the formation and stabilization of new synapses (Ullian et al., 2001; Slezak and Pfrieger, 2003; Hama et al., 2004; Nishida and Okabe, 2007). As it will be reviewed below, uPA and uPAR are found in all cellular components of the tripartite synapse, and synaptic plasticity induced by uPA-uPAR binding in axonal boutons, dendritic spines and perisynaptic astrocytes has a direct impact on synaptic repair following an ischemic injury.

Urokinase-Type Plasminogen Activator and Urokinase-Type Plasminogen Activator Receptor in the Presynaptic Terminal

During development uPA plays a central role in the formation of the presynaptic terminal. Indeed, uPA and uPAR expression coincides with the onset of axogenesis in the early stages of development (Dent et al., 1993), and in mature neurons the protease and its receptor are found in the axonal bouton (Merino et al., 2017). Our early studies show that uPAR expression increases in filopodia of axonal growth cones that re-emerge from a mechanical injury or that have suffered an ischemic insult, and that treatment with recombinant uPA (ruPA) promotes the formation of new growth cones and axons in the injured border and in the ischemic area, respectively, by a

mechanism that does not require plasmin generation (Merino et al., 2017). Importantly, this work also shows that LRP1 mediates the effect of uPA-uPAR binding on axonal growth. Surprisingly, in this system LRP1 does not act as an endocytic receptor but instead as a cell signaling receptor that transduces to the intracellular space signals triggered by uPA-uPAR binding on the surface of the injured axon. More specifically, we found that LRP1 promotes the recruitment of β1-integrin to the plasma membrane of the damaged axon, and that this leads to axonal regrowth via β1-integrin-induced Rac1 activation and Rac1-mediated reorganization of the actin cytoskeleton. In line with these observations, several groups have shown that Rac1 activation is crucial for the establishment of the cytoskeletal changes required for the development of synaptic plasticity in hippocampal learning and memory (Haditsch et al., 2009, 2013; Oh et al., 2010; Tejada-Simon, 2015). Therefore, these data indicate that uPA-uPAR binding promotes axonal repair via its ability to induce presynaptic plasticity in the ischemic brain.

Effect of Urokinase-Type Plasminogen Activator-Urokinase-Type Plasminogen Activator Receptor Binding in the Postsynaptic Terminal

The postsynaptic compartment is assembled by dendritic spines, which are protrusions that receive most of the excitatory input in the brain (Kasai et al., 2010) and are the locus for the development of synaptic plasticity (Sala and Segal, 2014). Indeed, the high motility of dendritic spines and their ability to rapidly change their shape and size in response to variations in synaptic activity, bestow on them a central role in the conversion of short-term alterations in synaptic strength into long lasting morphological changes (Yuste and Bonhoeffer, 2001). Cerebral ischemia has a harmful impact on the structure and function of dendritic spines (Zhang et al., 2005; Li and Murphy, 2008), which has a deleterious effect on synaptic function and neurological outcome. More specifically, following the onset of the ischemic injury dendritic spines are replaced by dilatations known as dendritic varicosities. Interestingly, while some spines re-emerge from these varicosities during the recovery phase, others never recuperate, leaving behind a smooth and spineless dendrite unable to sustain synaptic activity (Zhang et al., 2005; Wu et al., 2014).

Our early studies indicate that the expression of uPAR increases in those varicosities from which dendritic spines re-emerge after the end of the ischemic injury. Furthermore, we found that the re-emergence of dendritic spines and the associated improvement in neurological outcome are significantly impaired in mice genetically deficient on either uPA or uPAR, or in which a 4 amino acids mutation in the growth factor of uPA abrogates its binding to uPAR while preserving other functions of the protease and its receptor ($Plau^{GFDhu/GFDhu}$) (Connolly et al., 2010). Remarkably, intravenous treatment with ruPA after the end of the ischemic injury induced the re-emergence of dendritic spines and improved neurological function in $uPA^{-/-}$ and $Plau^{GFDhu/GFDhu}$, but not in $uPAR^{-/-}$ mice (Wu et al., 2014). Together, these data indicate that uPA binding to uPAR *in vivo* leads to the recovery of dendritic spines in the ischemic brain and improves neurological outcome after an ischemic injury. However, it is important to acknowledge the lack of experimental evidence linking dendritic spine recovery and improved neurological function. Nevertheless, it could be postulated that the repair of dendritic spines leads to restoration of synaptic contacts damaged by the ischemic lesion, and that in turn this reestablishes the network activity lost to the ischemic insult. Importantly, here is important to keep in mind that in contrast to cerebral ischemia, an increase in the number and motility of dendritic spines may also be associated with aberrant circuit formation and worse neurological outcome, as it has been demonstrated in different experimental paradigms of post-traumatic epilepsy (Wong and Guo, 2013). However, after taking into account these considerations, the data discussed here indicate that treatment with ruPA may be a potential therapeutic tool to promote neurological recovery among ischemic stroke patients. Regardless, future studies are warranted to determine whether ruPA treatment also promotes neurorepair in other pathologies such as post-traumatic seizures.

Independently of these considerations, a mechanistic approach to these data indicated that, as described above for the presynaptic terminal, uPA-uPAR binding also induces the reorganization of the actin cytoskeleton in the postsynaptic compartment. More specifically, these studies showed that uPA increases the abundance of profilin and phosphorylation-induced inactivation of cofilin, and that this sequence of events leads to an increase in F-actin abundance and the subsequence formation of filopodium and dendritic spines (Wu et al., 2014). These observations are of pivotal importance because the repair of synapses damaged by an ischemic injury requires the reorganization of the synaptic cytoskeleton (Hofmeijer and van Putten, 2009).

A closer look at the mechanism whereby uPA-uPAR binding reorganizes the cytoskeleton in dendritic spines showed that uPA increases the expression of ezrin, a member of a group of evolutionary conserved proteins that regulate the reorganization of the actin cytoskeleton (Fehon et al., 2010). Our data show that uPA-uPAR binding not only increases the abundance of ezrin but also induces its activation by phosphorylation. The *in vivo* significance of these findings was underscored by the observations that the expression of ezrin increases in the ischemic tissue during the recovery phase from an ischemic stroke in Wt, but not $uPA^{-/-}$, $uPAR^{-/-}$ or $Plau^{GFDhu/GFDhu}$ mice (Merino et al., 2018).

As stated above, uPAR is anchored to the plasma membrane via a GPI tail. However, because it lacks transmembrane and intracellular domains, it needs a co-receptor to activate cell signaling pathways (Blasi and Carmeliet, 2002). Interestingly, we have found that while β3 integrin subunit is the coreceptor that mediates the effect of uPA on dendritic spines recovery, β1-integrin is required for uPA-induced axonal recovery. In other words, these data reveal that the integrin subunit (β3 or β1) defines the compartment over which uPA/uPAR binding has an effect (postsynaptic or presynaptic, respectively). Notably, we found that β3-integrin induces the recruitment to the postsynaptic density of the intercellular adhesion molecule-5 (ICAM-5), which is known to promote the recruitment of ezrin to the plasma membrane (Ning et al., 2013). Furthermore, β3-integrin not only promotes the membrane recruitment of ezrin (via ICAM-5) but also induces its activation by phosphorylation. As observed in the presynaptic terminal, these events lead to the polymerization of new actin in the postsynaptic compartment and, surprisingly, this caused not only the re-growth of dendritic spines but also the formation of new branches in the proximal dendritic tree (Merino et al., 2018). The translational importance of these findings is underscored by the observation that the described effect of uPA on dendritic spine recovery in the ischemic brain is abrogated by siRNA-induced ezrin downregulation. Indeed, these results suggest that manipulating the expression of ezrin with may

be a potential therapeutic tool to promote the repair of dendritic spines in the brain that has suffered an ischemic stroke. Furthermore, experimental work with an *in vivo* model of cerebral ischemia showed that the formation of new dendritic spines and recovery of axonal growth cones (described above) induced by binding of either endogenous or recombinant uPA to uPAR, leads to the formation of new synapses in the area surrounding the necrotic core (Merino et al., 2018).

Binding of Neuronal Urokinase-Type Plasminogen Activator to Astrocytic Urokinase-Type Plasminogen Activator Receptor Induces the Formation of the Tripartite Synapse

As stated above, astrocytes are part of the tripartite synapse, and as such are capable of inducing synaptic plasticity via various mechanisms including the formation and maintenance of new synaptic contacts, and the regulation of the concentrations of glutamate in the synaptic cleft and the population of AMPA receptors in the postsynaptic density (Barker and Ullian, 2010; Chung et al., 2013, 2015). Importantly, these mechanisms are also involved in neurorepair following an ischemic injury (Murphy and Corbett, 2009). Interestingly, although uPAR is abundantly found in astrocytes, neurons but not astrocytes release uPA during the recovery phase from an ischemic injury (Diaz et al., 2017). These observations suggest that uPA-uPAR binding mediates a crosstalk between neurons and astrocytes. Our studies show that hypoxia and ischemia induce the recruitment of uPAR to the astrocytic plasma membrane, and that treatment with uPA induces astrocytic activation in wild-type but not uPAR$^{-/-}$ astrocytes (Diaz et al., 2017). Because neurons but not astrocytes release uPA during the recovery phase from a hypoxic/ischemic injury, these data suggest that by releasing uPA, damaged neurons are able to activate astrocytes in the vicinity of the injured synapses. We found that the effect of uPA-uPAR binding on astrocytic activation is mediated by ERK1/2-induced phosphorylation and nuclear translocation of the signal transducer and activator of transcription-3 (Diaz et al., 2017).

Our studies indicate that astrocytes activated by uPA-uPAR binding release thrombospondin-1, a member of a family of large extracellular proteins known by their ability to promote synaptogenesis (Ullian et al., 2001; Christopherson et al., 2005). Accordingly, our work shows that uPA-activated astrocytes induce synaptic repair in neurons exposed to hypoxic/ischemic conditions and that this effect is abrogated by TSP1 antagonism. More importantly, our data indicate that the interaction between astrocytic TSP1 and neuronal LRP1 mediates the synaptic restorative effect of uPA (Diaz et al., 2017). In addition to these findings, our studies show that as described in the presynaptic terminal, uPA also activates ezrin in astrocytes, and that this leads to the formation of thin elongations known as peripheral astrocytic processes that upon embracing the synapse protect its integrity from the harmful effects of a hypoxic/ischemic injury (Diaz et al., 2017). Importantly, the formation of peripheral astrocytic processes not only protects and repair the synapse, but also is crucial for the regulation of synaptic connectivity (Bernardinelli et al., 2014). Thus, the formation of peripheral astrocytic processes is another mechanism whereby uPA induces synaptic plasticity and synaptic protection. These observations are in line with experimental work indicating that glial cells are highly mobile, and that their contact with the pre- and postsynaptic compartments is crucial for synaptic function and circuit formation (Akiyoshi et al., 2018; Wake et al., 2019). More importantly, they suggest that the interaction between the synapse and glial cells is mediated by uPA binding to uPAR.

Conclusions and Future Directions

The studies discussed above indicate that uPA-uPAR binding promotes synaptic repair following an ischemic injury by its capacity to induce structural and functional changes in the axonal bouton, dendritic spine and perisynaptic glia (**Figure 1**). These findings have high translational relevance because they indicate that treatment with ruPA may be a successful therapeutic tool to promote neurological recovery among ischemic stroke patients. However, before moving these findings to the clinic is important to investigate whether or not the generation of new synaptic contacts induced by uPA-uPAR binding leads to the formation of aberrant tracts that may have harmful long-term consequences, such as seizures, aberrant innervation and pain. In that regard, it is important to acknowledge lessons learned from reactive plasticity in animal models of temporal lobe epilepsy in which the formation of new synapses contributes to the spread of epileptogenic discharges (Buckmaster et al., 2002). Regardless of these considerations, the data discussed above indicate that uPA-uPAR binding induces plasticity in all the cellular compartments of the tripartite synapse, and that this sequence of events are crucial to repair the synapse that has suffered an ischemic injury.

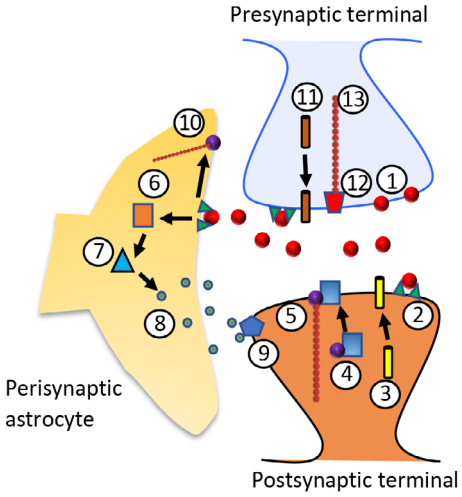

Figure 1 Schematic representation of the role of uPA in the tripartite synapse.
uPA released from the presynaptic terminal during the recovery phase from an ischemic injury (1; red circles) interacts with uPAR (green triangles) on the postsynaptic compartment (2), axonal bouton and neighboring astrocytes. uPA-uPAR binding on the postsynaptic terminal induces the membrane recruitment of β3-integrin (3; yellow cylinders), β3-integrin-mediated recruitment of ICAM-5 (4; blue squares), and ICAM-5-mediated recruitment of ezrin (5; purples circles), that then reorganizes the actin cytoskeleton in the postsynaptic terminal (5; chain of red circles). In perisynaptic astrocytes, uPA-binding to uPAR induces ERK ½ activation (6; orange squares), ERK ½-mediated STAT-3 activation (7; blue triangles), and the release of TSP1 (8; small green circles), that upon its interaction with LRP1 in the postsynaptic terminal (9; blue pentagon) promotes synaptic recovery. Furthermore, uPA-uPAR interaction in astrocytes induces the membrane recruitment of ezrin (10; purple circles) with the resultant generation of new actin bundles (chain of red circles) and the formation of peripheral astrocytic processes. uPA-uPAR binding on the presynaptic terminal promotes the membrane recruitment of β1-integrin (11; dark red cylinders), that induces Rac1 activation (12; red polygon) and Rac1-mediated reorganization of the actin cytoskeleton (13; chain of red circles) with the subsequent repair of the damaged axon. ICAM-5: Intercellular adhesion molecule-5; uPA: urokinase-type plasminogen activator; uPAR: urokinase-type plasminogen activator receptor.

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