Neuroprotection and neurorestoration: Ready for translation to clinics?[1]

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Summary

Our understanding of reorganisation processes in the ischemic brain has considerably increased recently. In the subacute stroke phase, tissue remodeling takes place in the vicinity of ischemic lesions, where inflammatory changes, astrocytic reactions, microglial responses and secondary neuronal degeneration are noticed. Injury processes can be successfully modulated by restorative therapies, which induce anti-inflammation, inhibit glial scar formation, enable the reorganisation of white matter tracts and prevent delayed neuronal injury. Plasticity-promoting therapies promote neurological recovery by enhancing axonal sprouting in lesion-remote brain areas rather than in previously ischemic tissue. This observation suggests that the recovery potential of the damaged tissue is limited even under conditions of mild cerebral ischemia. Careful proof-of-concept strategies are needed in the future to enable translation of experimental findings to clinics.

Key words: stroke; neuroregeneration; neuroplasticity; neurological recovery

With the recent extension of time windows, thrombolytic therapies have recently made considerable progress in the treatment of ischemic stroke [1]. As such, the percentage of patients thrombolysed is steadily growing, reaching approximately 20% or even more in well established stroke centres. Even though, with this increased awareness the time delay at which patients enter our hospitals is getting smaller and smaller which should lead to a further increase in thrombolysis rates, there are still no therapeutic options available for the majority of stroke patients. This raises the question regarding how brain damage can be successfully prevented and neurological recovery supported once a stroke has occurred.

Neuroprotection strategies

Strong efforts have been made in the past to translate neuroprotection therapies from bench to clinics. Despite numerous animal studies, in which survival promoting effects of various drugs were shown in different stroke models and species, clinical studies with neuroprotectants were so far disappointing [2]. As such, there is still no survival promoting therapy available that allows prevention of the progression of structural brain damage. A summary of strategies evaluated and examples of compounds tested is given in table 1.

Table 1
Neuroprotection strategies evaluated in the past in human stroke patients. Pharmacological strategies and examples of compounds tested. Note that all studies were negative.

Pharmacological strategy	Compounds tested
NMDA antagonists (competitive / non-competitive)	Selfotel, eliprodil, aptiganel
AMPA antagonists	ZK200775
GABA agonists	Clomethiazol
Glycine antagonists	GV150526
Free radical sacavengers	Tirilazad, NXY059
Calcium channel blockers	Nimodipin, piracetam
Sodium channel blockers	619C89
Growth factors	Erythropoietin*
Monoclonal antibodies against ICAM-1	Enlimomab

* Failed because of combination with thrombolytics. An earlier monocentre monotherapy study had shown structural neuroprotection and improved functional neurological recovery in erythropoietin-treated patients.

A major limitation of neuroprotection strategies is the short time window. As such, an efficacy of therapies can be expected only within 3 to a maximum of 6 hours after stroke onset. As such, future concepts should consider neuroprotectants mostly as add-on therapy for thrombolytics.

The fact that the combination of neuroprotectants with thrombolytics is not trivial, was recently revealed by the German erythropoietin (Epo) multicentre trial, which showed an increased mortality in patients receiving Epo in addition to thrombolytics [3]. The detrimental effect of Epo was most likely related to an exacerbated blood-brain barrier breakdown – namely via activation of matrix metalloproteases – in tissue-plasminogen activator treated animals [4].

Restorative strategies

The limited time window of neuroprotectants illustrates the need for strategies which are still efficacious when acute

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injury has developed. Unlike neuroprotection, restorative therapies are aimed at the remodeling of damaged brain tissue rather than the preservation of the tissue at risk. This implies that the therapeutic benefit is not immediate. It evolves progressively over several weeks, accompanied by neurological recovery processes which also present in a delayed fashion.

Experimental studies, over the past five years, have pointed out that the ischemic brain responds highly dynamically to strokes. As such, the lesion itself shows reorganisation phenomena, and tissue remodeling also takes place in brain areas distant to the brain lesion.

Shortly after the stroke, reactive astrocytes appear in the stroke lesion, releasing pro- and anti-inflammatory cytokines attracting blood borne leukocytes to migrate into the injured tissue. Microglial cells are activated, which are involved in the removal of cell debris. These responses trigger secondary degenerative changes in the brain tissue [5] resulting in the delayed loss of perilesional neurons and tissue shrinkage, at the same time setting the stage for subsequent plasticity processes.

Cell based and growth factor based restorative therapies inhibit inflammatory responses of the brain tissue, attenuating reactive astrogliosis and glial scar formation, at the same time as preventing microglial activation and secondary neurodegeneration [5].

The stroke itself induces axonal plasticity in the ischemic hemisphere, namely in the pyramidal system (Reitmeir et al., submitted). Lesion-sided sprouting however has limited consequences for neurological recovery, as it is hardly associated with motor improvements. Interestingly, growth factors do not further increase axonal sprouting in the injured hemisphere, but promote lesion-remote plasticity of the contralesional pyramidal tract.

Pitfalls

For the successful implementation of neurorestorative therapies, potential pitfalls in the translation from bench to bedside should be carefully considered. Drug interactions are complex. Without experimental data, they can hardly be predicted, as revealed by the recent German Epo multicentre trial [3]. Stroke patients are often multimorbid, receiving various medications against different medical conditions. Our research strategies so far have not adequately considered the complexities of multiple pharmacological therapies, and perhaps it is not unlikely that drug interactions may represent a reason for study failures in human patients.

A major problem of acute neuroprotection studies were unexpected side effects, which were not anticipated in animal studies. As such, hints for unfavourable drug actions should be carefully recognised in preclinical studies. Recent plasticity studies have shown that neuronal plasticity and survival may not be regarded independent from each other in the ischemic brain. As such, survival effects of plasticity-promoting compounds should not be neglected.

Evidence for unfavourable consequences of axonal growth promotion were recently obtained in animals submitted to transient focal cerebral ischemia, when the axonal growth inhibitor NogoA was blocked with monoclonal antibodies before, but not after the stroke [6]. This study revealed an exacerbation of ischemic injury that was mediated by direct effects of RhoGTPases on cellular stress responses and apoptotic pathways [6]. The approach in that study was clinically irrelevant, as a pretreatment strategy was used. Yet it reminds us of crosslinks between neuronal plasticity and neurodegeneration pathways.

Transient focal cerebral ischemias represent the majority of strokes in clinics, as spontaneous reperfusion takes place in approximately 50% of patients within 24 hours reperfusion. In view of potential consequences of plasticity promotion for cell survival, plasticity promoting therapies should be evaluated both in models of permanent and transient focal cerebral ischemia.

Conclusions

Careful proof-of-concept strategies need to be developed in the future for the translation of stroke therapies from the bench to bedside. As such, exactly the same conditions as those evaluated in the lab should be evaluated in clinics. Changes of protocols, such as assessment of neuroprotectants in thrombolysed patients with compounds so far never evaluated after thrombolytic therapy in animals, should no longer be performed, as they risk the success of otherwise promising research strategies. As such, failures of neuroprotection studies may instruct us how to set up translation strategies in the future. Based on our present knowledge and insights, future therapies might focus more promisingly on the post-acute rather than the acute stroke phase.

References

1 Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al.; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359(13):1317–29.

2 Hermann DM, Bassetti CL. Implications of ATP-binding cassette transporters for brain pharmacotherapies. Trends Pharmacol Sci. 2007;28(3): 128–34.

3 Ehrenreich H, Weissenborn K, Prange H, Schneider D, Weimar C, Wartenberg K, et al.; EPO Stroke Trial Group. Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke. 2009; 40(12):e647–56.

4 Zechariah A, Elali A, Hermann DM. Combination of tissue-plasminogen activator with erythropoietin induces blood-brain barrier permeability, extracellular matrix disaggregation, and DNA fragmentation after focal cerebral ischemia in mice. Stroke. 2010;41(5):1008–12.

5 Bacigaluppi M, Pluchino S, Peruzzotti Jametti L, Kilic E, Kilic U, Salani G, et al. Delayed post-ischaemic neuroprotection following systemic neural stem cell transplantation involves multiple mechanisms. Brain. 2009; 132(Pt 8):2239–51.

6 Kilic E, ElAli A, Kilic U, Guo Z, Ugur M, Uslu U, et al. Role of Nogo-A in neuronal survival in the reperfused ischemic brain. J Cereb Blood Flow Metab. 2010;30(5):969–84.