ARE NEUROPROTECTION AGENTS STILL AN OPTION FOR ACUTE ISCHEMIC STROKE (AIS)?
YES
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Neuroprotection in acute stroke depends on 2 preconditions. Firstly, neuroprotection does not work without recanalisation. Only when the occluded vessel can be recanalized - which happens either spontaneously (about in 20-25%) or by means of thrombolysis (with iv rtPA in about 50% of cases) - protection of neurons can become effective. The other condition for effective neuroprotection is time-dependency that implies that neuroprotection has to be applied within a time window that is similar to the one for thrombolyis such as within the first few hours following a stroke.
In the last decade or two numerous neuroprotection clinical trials have been performed, all of which have failed. The reasons for these failures are several. Often the rationale for a trial was based on stroke models in animals that do not closely resemble the condition in human stroke patients. Often substances were tested hat had either not undergone proof-of-principle trials or had failed to show any effect at all in early clinical testing. Furthermore, neuroprotectants were applied within a time-window that was not responsive to change anymore and where the status of the vessels as open or occluded had not been considered.
Therefore, revised criteria have been published for preclinical testing of neuroprotection. These include, among others, that a test is performed in 2 different animal species, in two different (independent) labs, that older and stroke prone animals should be used wherever possible and that randomisation to controls and blinded evaluation should also be considered in such experiments.
Recently, a concept of a second penumbra has been put forward which enables us to understand early mechanisms of recovery. Some of these mechanisms are interwoven with neuroprotection in the strict sense. The cross-talk between neuronal and microglial cells include mechanism of membrane stabilization and reuptake of synthesis action as well as promotion of angiogenesis. This is the basis for preserving and restoring function of the neurovascular units. Thus, neuroprotection also has some overlap with early recovery.
Neuroprotection has been estimated to be most effective when its effects are multifactorial, that is directed at several mechanisms of the ischemic cascade. This is the case with a number of natural or recombinant biologicals. Complex compounds passing the blood brain barrier as well as smaller molecules targeted to stabilize neuronal function are presently being tested in clinical trials. In addition, several physical principles such as hypothermia and transcranial laser therapy, both of which have undergone and passed proof-of-principle testing, are currently being tested in large, international trials, the results of which will become available within the next few years.
In conclusion, the current and modified neuroprotective concept in brain ischemia allows new trials to be performed in humans that bear a promising potential for success.