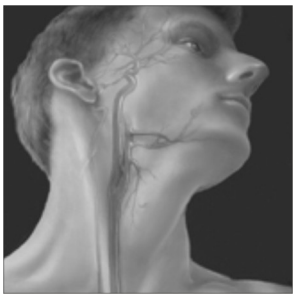
REVIEW PROF-879

STROKE;
THERAPEUTIC POTENTIALS



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ABSTRACT... asadaliazeemi2001@yahoo.com Stroke was defined according to WHO criteria as rapidly developing symptoms and / or signs of focal and at times global loss of cerebral function with no apparent cause other than that of vascular disease[1]. Stroke is grossly divided into either[2] 1). Thrombotic. 2). Embolic. 3).Hemorrhagic type (Which may be either intra cerebral bleed or subarachnoid hemorrhage). The brain, like other organs of the body, requires an adequate vascular system in order to supply it with nutrients and oxygen and to remove metabolic wastes and carbon dioxide. Stabilization of medical problem with careful monitoring, and active prevention and timely management of secondary complications are of the utmost important for reducing stroke morality rates and avoiding further ischemic brain injury. For the ischemic cerebral lesion itself, as yet no treatment or combination of treatment has been established to be universally effective[3]. However, current studies allow for the following 5 potential therapeutic areas to be identified.

ACUTE CEREBRAL INFARCTION WITH IMPEDING NECROSIS

Dead neurons cannot be revived so that the best treatment of infraction is prevention. It has shown that the major risk factors for stroke are either preventable or controllable. Smoking, hypertension, elevated serum lipid levels and diabetes mellitus all increase the risk cardiac disease and stroke. In turn, these risk factors are often associated with high calorie diet, abdominal obesity, sedentary life habits, psycho social stress, lack of physical exercise, and excessive alcohol consumption. Therefore, it is possible to forestall the development of stroke in a population through the propagation and promotion of healthy life styles.

a. Prevention and control of the following reversible risk factors

Hypertension, smoking, overweight, diabetes mellitus, hyperlipidemia and cardiac risk factors[4]. Adoption of health promoting dietary habits, regular physical exercise and a supportive psycho social environment are prerequisites. These prevention and control of risk factors among children and young adults should be stressed[5].

b. Targeted preventive treatments

Calcium channel blockers should be administered in the acute stage of the subarachnoid haemorrhage to prevent vasospasm, there by reducing the risk of infraction. Anti-thrombotic therapy should be instituted in the patients with potential cardiogenic embolic atrial fibrillation to prevent cerebral embolism[6].

Selective carotid endarterectomy should be carried out in symptomatic internal carotid artery stenosis exceding 70% of the lumen. Short term neuro-protective therapy is advisable in major cardiovascular surgery during which cerebral circulation is likely to be compromised[7.] Long term anti-platelet therapy should be begun in individual with TIAs and multiple risk factor[8].

THE ISCHEMIC PENUMBRA

The region surrounding the central ischemic cores of cerebral infraction remains viable for a limited time. Haematologic event such as platelet adhesion, aggregation and activation, endothelial activation, coagulation and fibrinolysis, accumulation and activation of white blood cells, acidosis prostaglandin derangements, leukotriene followed by lipolysis, proteolysis, intracellular entry of Ca^{+2}, damage by free radicals and altered expression of genes all play a part in the progressive process of cell necrosis after cerebral ischemia[9].

Many drugs and therapies have been proposed to be effective against these events in the ischemic casade.

The right patient indication, the appropriate time window, the optimal dosage by the most effective route, and best protocols for testing these therapies have yet to be determined, if they can finally be proved of benefit[10]. Of all those therapies proposed, the concept of thrombolysis is most attractive.

Therapeutic effect of thrombolytic is impressive, but the complication rate from cerebral haemorrhage is often higher than in the untreated control patients.

Laboratory and clinical observation suggest that a reversible ischemic penumbra exist for a period of less than 2 or 3 hrs. In order to salvage as many endangered neurons as possible, effective therapy should be instituted at the earliest possible time[11].

The mechanism underlying cerebral ischemic injury are manifold, but the various factors seem to be intricately interrelated so that two or more drugs, each with its specific targeting effect administered in series and/or in parallel, appear to be more logical than relying on one drug applied to all ischemic stroke patients[3]

ACCELERATED NEURONAL APOPTOSIS

It has recently been shown that, in addition to necrosis, cerebral ischemia may lead to accelerated neuronal apotosis. Cerebral ischemia produce as influx of calcium ions into neurons, activating protein kinesis and inducing rapid and transient expression of genes termed immediate early genes (IEGs), including c-fos, fosB, c-jun, jun-B, NGFI-A(Krox-24), NGFI-B(NUrr77) and fra.

The IEG proteins produced by translation of these genes may active late-effector genes (LEG) transcription, resulting in the synthesis of late-effector proteins, including neurotransmitters, enzymes, proteins and growth factor, IEG, may be involved in the induction of programmed cell death (PCD) or in the production of neurprotection and recovery after, following ischemia.

The regulation of PCD is dependent on a complex balance between cell-death enhancing and cell-death suppressing homologous. Current research is directed to find measure that positively influence nerve cell apoptosis after ischemia[12].

AUTO PROTECTIVE REPAIR MECHANISM

It is now recognized that cerebral ischemia may lead to activation of auto protective repair mechanism normally existing in the brain, which may counteract the cell killing responses of ischemia.

Heat shock patients (HSPs) are stress proteins induced for longer, than 10 hours after ischemia. HSPs may be factors in neuro-protection against ischemia Trophic factors are produced, released and taken up by the

neurons or glial cells. Focal application of nerve growth factor, insulin like growth factor-I and TGF-B have been reported to protect neurons against ischemic injury, although not all reports in a agreement[3].

And intricate auto protective system involving activation of GABA-B and adenosine receptors able to reduce the extent of anoxic injury has recently been demonstrated in white matter[3].

On exposure to anoxia, they are released initiating a cascade of intracellular pathway involving the activation of GTP- binding membrane protein (G-protein) and protein kinase C (PKC). Specific GABA-B receptor antagonist, baclofen or adenosine receptors antagonist theophyline, significantly reduced recovery after anoxic injury in white matter as compared to controls.

Recovery of white matter function following anoxia is improved by perfusion with the GABA intake inhibitor, nipecotic acid, or the adenosine uptake inhibitor, propentophyllin, ro raise the level of GABA or adenosine in the extra cellular space. Possible pharmacological manipulation of this mechanism might be useful for ischemic stokes predominately involving white matter[13].

DOWN REGULATED BRAIN REGIONS

If infarctive areas were the only brain tissues available for treatment, any further recovery or improvement of neurological deficit would not be possible after the acute stage of ischemia. Neurological deficits in many patients could in improve even many years later [14].

It is hypothesized that neurons with intimate connection with the infracted area becomes less active or inactive due to lowered synaptic activation. The down regulated neurons in these low perfused remain viable long after the initial ischemic event.

There blood supply is nerve compromised by the ischemic insult. They are disconnected and down regulated normal neurons. Once these brain regions can be activated to up-regulate, defective neurons functions improves and focal cerebral flow increases in proportion to the increases of the induced regional cerebral metabolic rates [15].

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