PHARMACOLOGICAL CLASSIFICATION OF CENTRAL NERVOUS SYSTEM NEUROPROTECTIVE THERAPIES

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ABSTRACT

A lot of neurological disorders still do not have an elucidated etiology, but the latest research brought insight in the pathologic mechanisms and made possible the identification of neuro-toxic phenomena, such as free radicals and excito-toxic agents, with important roles in ischemic and degenerative neurological disorders. Consequently, the therapeutical strategies of neuroprotection currently have the aim to prevent neuronal death and protect against neurodegeneration and neurotoxins.

The main diseases where research was done and neuroprotective therapy has been investigated or used are: cerebrovascular disorders (infarction or hemorrhage), trauma (brain or spinal cord injuries), neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), epilepsy and multiple sclerosis.

A pharmacological classification of neuroprotective agents is now available, and have been tested in animal experiments and clinical trials, like: adenosine re-uptake blockers, antiepileptic drugs, anti-inflammatory agents, apoptosis inhibitors (caspase or calpain inhibitors, poly ADP-ribose polymerase inhibitors), free radical scavengers or antioxidants, gamma-amino-butyric acid agonists, glutamate antagonists, N-methyl-D-aspartate antagonists, competitive and noncompetitive N-methyl-D-aspartate receptor antagonists, kainate antagonists, glycine site antagonists, glutathione, hormones, ion channel blockers, leucocyte adhesion inhibitors, neuroimmunophilins, neuropeptides, neurotrophic factors and enhancing agents, nitric oxide inhibitors, nootropics, phosphodiesterase inhibitors, phosphatidylcholine precursors, gene therapy, hyperbaric oxygen therapy, hypothermia.

The clinical applications may be various, although research still goes on for developing new therapies and future will hopefully bring us new methods to improve the outcome in patients with neurological pathology, by decreasing the degree of their disability and by increasing the quality of life.

The neuroprotection concept interacts with all three phases of the management of central nervous system diseases: prevention, the active phase of the disease, and the chronic or recovery phase.

Key words: neuroprotection, key molecules, pathogenic mechanisms, clinical applications

PHARMACOLOGICAL CLASSIFICATION

There is now available a pharmacological classification of neuroprotective agents, which have been tested in animal experiments and clinical trials, like:

1. Adenosine re-uptake blockers
- Dipyridamole
- Propentofyline: neuroprotective glial cell modulator with several effects like:
  - it blocks adenosine transports
  - inhibits cyclic adenosine monophosphate and cyclic guanosine monophosphate-phosphodiesterases
  - inhibits cytotoxic functions of activated microglia
  - modulates astrocytic functions by stimulating nerve growth factor synthesis and secretion

2. Antiepileptic agents
- Phenytoin: a sodium channel blocker which provides neuroprotection by stopping the sustained influx of intracellular sodium through voltage-gated sodium channels who is an important event in the cascade leading to degeneration of axons
- Topiramate: has a neuroprotective action which seems to be directly related to its inhibitory effect on the mitochondrial permeability transition pore,with direct effects of the drug on mitochondrial oxidative phosphorylation and a protective effect on hippocampal mitochondria against an external calcium challenge

3. Anti-inflammatory agents
- Dipyrone
- Doxycycline
- Gabexate mesilate
- Methylprednisolone (used in high-dose as a neuroprotective agent in patients with spinal cord and brain injury)
- Synthetic fibronectin peptides

4. Apoptosis inhibitors
- Calpain inhibitors
- Caspase inhibitors
- Cycloheximide
- DP-beta 99(metal ion chelator)
- L-actylcysteine

- Poly-(ADP-ribosyl) polymerase inhibitors
- Transcription factor NF-KB

Apoptosis is an inherently programmed cell death, that mediates cell deletion in tissue homeostasis, embryological developement and several pathological conditions as stroke and neurodegenerative diseases.

- The calpain inhibitors have the aim to stop the pathway mediating apoptosis initiated by excitotoxicity and elevated Ca2+ levels, as it is known that calpain activity increases in traumatic brain injury, spinal cord injury cerebral ischemia and Alzheimer disease
- The caspase inhibitors are peptides that can also suppress apoptosis, because they are resembling the cleavage site of known caspase substrates. Their effect can be reversible or irreversible.
- The Poly (ADP-ribose) polymerase inhibitors have the aim to stop the complete deletion of a cell's energy levels, originated in an excessive activation of poly (ADP-ribose) polymerase, generated by nitric oxide, so that the neurotoxicity cascade and neuronal cell death is no longer active, having a neuroprotective effect in stroke and other disorders.

5. Barbiturates

- provides neuroprotection and suppression of cerebral metabolic rate, making possible a protection of neurons against ischemic injury caused by excitotoxicity

6. Cell transplants

- secreting neuroprotective substances: there were done experiments by using stem cell transplants to enhance recovery from cerebrovascular damage. Stem cells – found primarily in bone marrow or in embryonic tissue – have the ability to develop into any of the body's organ cells, including the brain. They are omnipotential cells that are highly flexible. Rat stem cells that are transplanted into both healthy and stroke-injured adult rats develop into neurons. Experiments showed that the stem cells grew in the area of stroke damage and formed connections with adjacent cells and that cortical stem cells can survive, multiply, and differentiate, and this growth depends on the local environment in which they are implanted.

7. Erythropoietin

8. Free radical scavengers or antioxidants

- AM-36(arylalkylpiperazine)
- Nicaraven
- LY 231617
- Dopamine D2 receptor agonists
- Neuroleptics: chlorpromazine
- Ebselen
- Idebenone
- Vitamins E and C
- Pyrrolopyrimidines
- Tirilazad mesylate
  - The cell damage caused by free radicals includes protein oxidation, DNA strand destruction, increase of intracellular calcium, activation of damaging proteases and nucleases, and peroxidation of cellular membrane lipids.
  - This intracellular damages can lead to the formation of prostaglandins, interferons, trinitrofluorenone-alpha and other tissue-damaging mediators, which can lead to disease if they are overproduced in response to the oxidative stress.
  - The antioxidant defense systems and cellular repair mechanism of the body can control in some way the damaging effects of the free radicals, and the natural antioxidants have been investigated as potential therapeutical agents, but with disappointing results.
  - The synthesized antioxidants were and still are tested in clinical trials, some without effects, and some demonstrating neuroprotective effects (dopamine agonists used in the treatment of Parkinson disease).
  - Neuroleptic drugs are powerful scavengers of hydroxyl radicals and also powerful inhibitors of iron ion-dependent liposomal lipid peroxidation, scavengers of organic peroxyl radicals and inhibitors of hem protein and hydrogen, peroxidations of arachidonic acid.

9. Gamma-amino-butyric acid agonists

They enhance gamma-amino-butyric acid A receptor responses, so that they have neuroprotective effects.

- Clomethiazole: a gamma-amino-butyric acid (GABA) agonist that appeared to have neuroprotective properties in preliminary studies.
- Ganaxolone: is a structural derivate of progesterone, without hormonal activity, from the class of epalons, neuroactive steroids which specifically modulate gamma-amino-butyric acid A receptors in the central nervous system. His neuroprotective effects were demonstrated in clinical trials for epilepsy and cerebral hemorrhage.

10. Gene Therapy

- There were done experiments using a genomic herpes simplex virus-based vector expressing

either neurotrophic factors or anti-apoptotic peptides for protecting neurons from a variety of insults
- A neurotrophic factor derived from gliall cell-line, delivered by a lentiviral vector system, can prevent nigrostriatal degeneration and induce regeneration in primate models of Parkinson disease
- Researchers have now shown that administering gene therapy (overexpression of neuroprotective heat shock protein 72 [HSP 72]) in the post-ischemic period of a rat stroke model protects hippocampal CA1 neurons from global cerebral ischemia

11. Glutamate antagonists
- Amino-methyl propionic acid antagonists
- LY300164
- YM872
- ZK-20077544
  - Glutamate is the principal excitatory neurotransmitter in the central nervous system. The excessive glutamate-mediated excitation is a main feature of acute cerebral infarction and in mediating apoptosis in neurodegenerative disorders, as also in traumatic injuries of the CNS.
  - It is understandable why the anti-excitotoxicity approach as neuroprotective effects had a great development.

12. N-methyl-D-aspartate antagonists
- Presynaptic glutamate blockade
- Enadoline
- NAALADase (N-acetylated-alpha-linked-acidic-dipeptidase) inhibitors: they act as anti-glutamate agents by inhibiting the enzyme at presynaptic levels and protect against neurodegeneration in vitro and in some in vivo animal models.

13. Competitive N-methyl-D-aspartate receptor antagonists
- 1-cis-2-carboxypiperidine-4-yl-propyl-1-phosphonate
- 2-amino-5-phosphonovalerate (APV): determines reducing of nitrite concentrations
- 2-amino-7-phosphoheptanoate(APH)

14. Noncompetitive N-methyl-D-aspartate receptor antagonists
- Ceresine (CP101,606): a novel NR2B subunit of N-methyl-D-aspartate receptor who showed a decrease of the serum and cerebrospinal fluid lactate concentrations after intravenous injection, in stroke models in animals, slowing the development of cytotoxic edema and the lowering the infarct volume
- Dextrophan
- Dextromethorphan
- Dexanabinol
- Gacyclidine
- Ketamine
- Magnesium
- Memantine: a glutamate blocker with anti-excitotoxic action and neuroprotective effects
- Phencyclidine

15. Non-N-methyl-D-aspartate excitatory amino acid antagonists
- 5-hydroxytryptamine agonist: activation of 5-HT receptors of the 5-HT(1A) subtype might help to control glutamate efflux and excitotoxic damage during ischemia in human cerebral cortex and is considered a pottential approach to neuroprotection in brain ischemia
- Lubeluzole: novel neuroprotective drug, which in previous in vitro and focal ischemia studies has been shown to inhibit nitric oxide synthesis, to block voltage-gated Na+-ion channels, and to inhibit glutamate release, as increases in extracellular glutamate during cerebral ischemia may play an important role in neuronal injury. He is effective in inhibiting extracellular glutamate accumulation during global cerebral ischemia, and has the potential to produce potent neuroprotection when instituted prior to an ischemic event
- Opioid receptor antagonists: Naloxone, Nalmefene

16. Glycine site antagonists
- ACEA 1021: glycine-site specific NMDA antagonist is an effective neuroprotective agent in animal models of cerebral ischemia
- GV150526: an antagonist of the glycine site of the N-methyl-D-aspartate receptor
- Polyamine site antagonists as Eliprodil and Ifenprodil: Polyamines and polyamine-dependent calcium influx play an important role in mediating the effects of excitotoxic amino acids at the N-methyl-D-aspartate (NMDA) receptor site. The polyamine-site NMDA receptor antagonist ifenprodil affords significant neuroprotection in a controlled cortical impact brain injury model and may hold promise for the discovery and treatment of the mechanism of delayed neurological deficits after traumatic brain injury

17. Glutathione
- It has cytoprotective effects with an important role in neuroprotection from neurotoxicity because he is a central component in the antioxidant defence of cells, Glutathione peroxidase-1 plays

an important regulatory role in the protection of neural cells in response to ischemia/reperfusion injury

18. Hormones

- Corticosteroids
- Estrogens
- Insulin

19. Hyperbaric oxygen therapy

- it relieves hypoxia, improves microcirculation, decreases cerebral edema, protecting the partially damaged tissue.

20. Hypothermia

- acts through several mechanisms as, preservation of high-energy phosphates needed for post-ischemic metabolic recovery, attenuation of release of neurotoxic excitatory amino acid glutamate into extracellular space, prevention of ischemic-induced inhibition of calcium and calmodulin-dependent protein kinase ll and protein kinase C, reduction of free radical formation during ischemia. Neuronal degeneration may be ongoing for months after a transient ischemic insult, and prolonged protective measures need to be instituted for long-lasting neuroprotective effects. Hyperthermia during recovery worsens ischemic damage, and processes associated with inflammation may contribute to the development of neuronal damage. An early and extended period of post-ischemic hypothermia provides a powerful and long-lasting protection if followed by treatment with anti-inflammatory/antipyretic drug.

21. Ion channel modulators

- Ca+ channel blockers: preventing Calcium overload is very important for neuroprotection
  - Nimodipine: it has cerebrovasodilatatory and neuroprotective effects, without altering peripheral circulation; it is effective in delaying cerebral deficits after subarachnoid hemorrhage
  - Ziconotide: is an N-type, neuron-specific calcium channel with a protective effect against focal ischemia through the inhibition of glutamate release from presynaptic sites. It is possible that it affects the release of other neurotransmitters, and showed protection against neuronal loss after global cerebral ischemia in animal models of stroke.
- Na+ channel blockers: down regulation of the Na channels is an effective way of reducing energy demand, because a large part of the energy consumed by the brain is used for the maintenance of ion gradients across cellular membranes, so that reducing the Na influx into the brain cells will preserve energy when ischemia is present. It also prevents the intrinsic neurotoxicity of the acute Na influx as well as the linked Ca2+ influx.
  - Carbamazepine, Fosphenytoin, Lamotrigine, Phenytoin, Riluzole: have demonstrated neuroprotective effects
- K+ channel opener: BMS-204352

22. Leukocyte adhesion inhibitors

- Leukocytes play an important role in ischemic injury of CNS by several mechanisms: direct microvascular occlusion after basement membrane adhesion, transendothelial migration with secondary tissue infiltration and neuronal cytotoxic injury. All these effects can be decreased by using special monoclonal antibodies directed against leukocyte adhesion receptors.
- Antibodies directed against the CD18 complex (beta2-integrin) which is responsible for endothelial adherence; the mouse models showed reduction of ischemic injury and decrease of leukocytes infiltration in the brain.
- Anti-ICAM antibodies (Enlimomab): the experimental models showed effects of reducing cerebral ischemia only when significant reperfusion injury is involved.
- Hu23F2G: humanized antibody that binds to and blocks the functions of the CD11/CD18 integrin (leukocyte adhesion receptors) which play an important role in inflammation via their regulatory effects on leukocyte adhesion, transmigration, and function.
- Neutrophil inhibitory factor (NIF): blocks the adherence to polymorphonuclear leukocytes dependent on both Mac-1 and LFA-1 integrins, so that it stops the subsequent migration into damaged tissue, so that it prevents the acute inflammatory response during reperfusion injury, which can exacerbate damage to the areas of the brain affected by stroke.
- Synthetic fibronectin peptides: corresponding to the cell-and heparin-binding sequences of fibronectin that disturb leukocyte adhesion molecules, so that they are effective in neuronal protection after transient focal cerebral ischemia in rats.

23. Neuroimmunophilins

- They have several mechanisms of action as: anti-inflammatory effects, inhibition of nitric oxide synthase activity, supression of apoptosis and supression of calcium-dependent signal transduction pathway that promotes interleukin-2 gene transcription in helper T-cells and direct neuronal action.

- Cyclosporin: has a protective effect by interfering with the energy-producing mitochondria, by blocking mitochondrial cytocrome C release and apoptotic cell death, and also by blocking the nitric oxide production
- Tacrolismus(FK-506): inhibits apoptosis
- FKBP (FK binding proteins)

24. Neuropeptides

- Alpha-melanocyte stimulating hormone
- Corticotropin-releasing hormone
- FPF 1070 (cerebrolysin)

25. Neurotrophic factors and enhancing agents

- AIT-082(Neotrofin): a cognitive-enhancing and neuroprotective drug which increases HO-1 immunoreactivity in neurons of the hippocampal formation and its connections including CA1-4, fornix, septal nuclei, hippocampal commissure, septohippocampal nucleus, fimbria, anteroventral thalamic nucleus, frontal and parietal cortex. The effect of Neotrofin on HO-1 appears to be at the transcriptional level, as suggested by an increase in HO-1 mRNA levels.
- Brain derived neurotrophic factor: neuroprotection arises, at least in part, via its ability to block the mechanism by which pathophysiological Ca2+ influx through the NMDA receptor causes membrane protein kinase C inactivation. He protects cortical neurons against apoptosis induced by camptothecin or serum deprivation and activates the extracellular-signal-regulated kinase (ERK) and the phosphatidylinositol 3-kinase (PI 3-kinase) pathways.
- Fibroblast growth factor
- Insulin-like growth factor: given in a novel, safer, intranasal infusion significantly reduces neurologic deficits (motor and sensory function) in a rat model of ischemic stroke. Less cerebral edema was noted. This form of therapy may offer promise in the treatment of acute ischemic stroke
- Nerve growth factor
- Pigment epithelium-derived factor

26. Nitric oxide inhibitors

- During pathologic conditions as stroke, calcium overload causes prolonged activation of the enzyme nitric oxide synthetase, with an excess amount of nitric oxide release which causes neural damage. Selective inhibition of neuronal nitric oxide synthetase and associated proteins as PIN-1 and CAPON will lead to a neuroprotective effect in ischemic cerebrovascular disorders, traumatic brain and spinal cord injuries and neurodegenerative diseases.
  - Aminoguanidine
  - Lubeluzole: is a benzothiazole derivative that has shown neuroprotective properties in different experimental models inhibiting glutamate release, nitric oxide (NO) synthesis and blocking voltage – gated Na+ and Ca2+ ion channels, which inhibits an increase in extracellular glutamate
  - Selective nNOS inhibitors

27. Nootropics

- FPF 1070(cerebrolysin): (CERE) is a potential neuroprotective agent that has effects on neuronal calcium metabolism and has neurotrophic effect
- Ginko biloba: is used as a neuroprotector and to enhance cognition in normal elderly, but whether or not it is able to reduce cognitive symptomatology or delay onset of Alzheimer's disease is still undetermined
- Piracetam

28. Phosphodiesterase inhibitors

- Denbufylline: a xanthine derivative with selective inhibitory activity on the phosphodiesterase (PDE) 4 isoenzyme; experiments showed that accumulation of adenosine-3',5'-monophosphate (cAMP) in the postsynaptic cell and/or in the presynaptic terminal produced by blockade of phosphodiesterases leads to enhanced synaptic transmission in the CA1 area of the hippocampus and ii) that a low KM, Ca2+/calmodulin-independent cAMP-phosphodiesterase is an important component involved in the regulation of the intracellular cAMP level at synapses of central nervous system neurons.

29. Phosphatidylcholine precursor

- Citicoline (CDP-choline): is an intermediate in the biosynthesis of phosphatidylcholine (PtdCho), which has shown beneficial effects in a number of CNS injury models and pathological conditions of the brain; the neuroprotective effects act by:
  - preserving cardiolipin (an exclusive inner mitochondrial membrane component) and sphingomyelin
  - preserving the arachidonic acid content of PtdCho and phosphatidylethanolamine
  - partially restoring PtdCho levels
  - stimulating glutathione synthesis and glutathione reductase activity
  - attenuating lipid peroxidation
  - restoring Na(+)/K(+)-ATPase activity.

These observed effects of citicoline could be explained by the attenuation of phospholipase A(2) activation.

CONCLUSIONS

The neuroprotection interacts with all three phases of the management of central nervous system diseases:

- Prevention: management of risk factors and institution of neuroprotection as prophylaxis before high risk procedures associated with hypoxia/ischemia, anticipated exposure to neurotoxins and in early or asymptomatic stages of neurodegenerative disorders.
- The active phase of the disease and: symptomatic management, treatment if available, and neuroprotection for minimizing the impact of initial insult and interfering with subsequent progressive mechanisms.
- The chronic or recovery phase of the disease: rehabilitation and long term neuroprotection in chronic evolving damages of CNS.

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