[S3-4] [4/18/2005(Mon) 15:30-16:00/Gumungo Hall B]

Targeting Signaling Pathways of Ischemic Brain Injury

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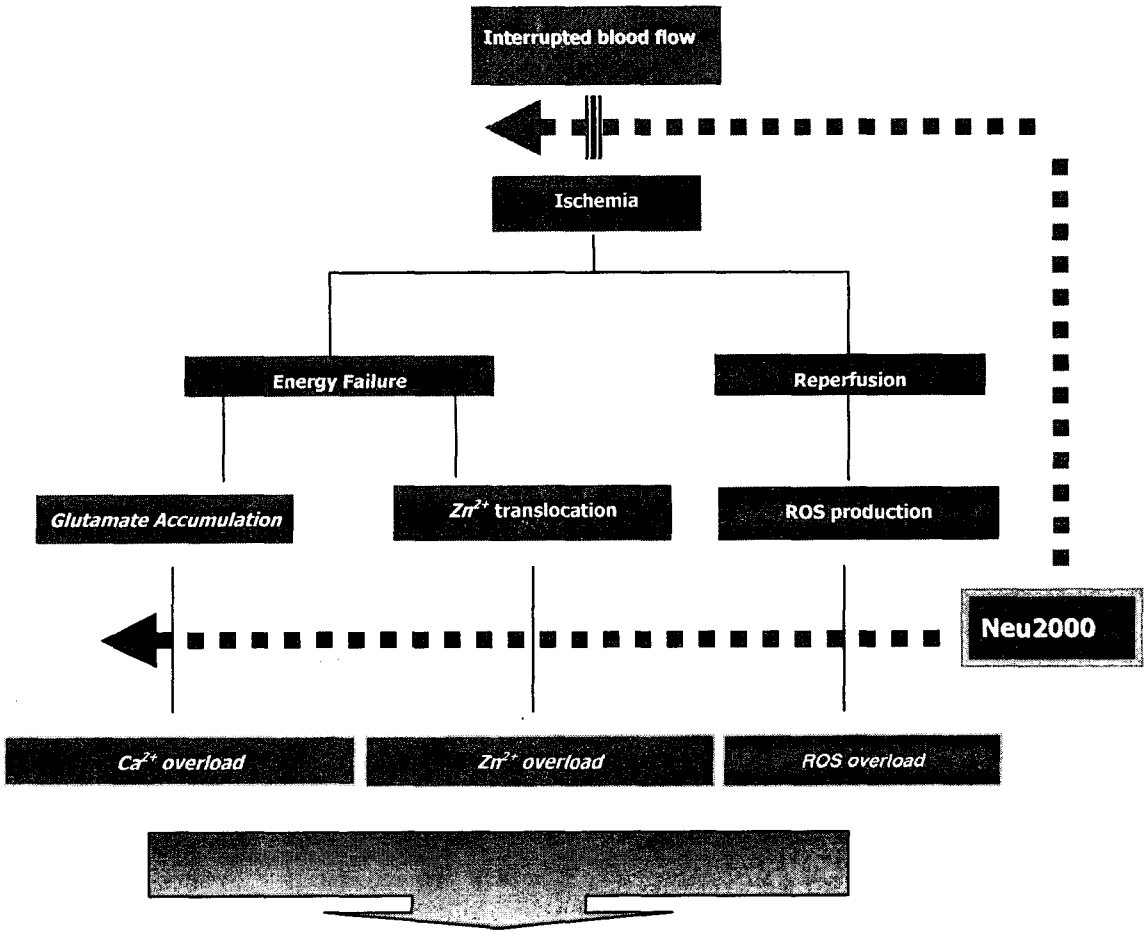
Interrupted blood supply to brain by local thrombosis, embolic particles, or rupture of blood vessels can cause primary neuronal death in the core areas, which is accompanied by the secondary death in the ischemic penumbra through activation of multiple death pathways. While thrombolytic and anticoagulant drugs are being used to enhance reperfusion and to modify coagulation, neuronal death occurs over hours and days following even a brief ischemic attack, and has been targeted for therapeutic intervention. The first line of interventional therapy stems from findings that excess activation of the Ca^{2+}-permeable ionotropic glutamate receptor sensitive to NMDA causes fulminant neuronal death following hypoxic-ischemic insults. Accordingly, a number of NMDA receptor antagonists have been developed and shown to reduce hypoxic-ischemic brain injury in various animal models. However, none of them have been beneficial in the clinical trials of ischemic stroke patients mainly due to the narrow therapeutic index and time window of NMDA receptor antagonists The latter appears to be associated with an additional insult to brain evolving after reperfusion or reoxygenation, which is triggered by cytotoxic free radicals generated primarily through mechanisms involving intracellular accumulation of free cations such as Ca^{2+}, Zn^{2+}, and Fe^{2+} as well as mitochondrial dysfunction. Thus, strategies targeting signaling cascades linked to both NMDA receptors and free radicals could help pave the way for novel medications that combat early and delayed neuronal death after hypoxic-ischemic brain injury. A novel neuroprotectant Neu2000 derived from aspirin and sulfasalazine has been developed to meet the therapeutic need for stroke.

Neu2000: The targeted drug for treating



Neuronal Death