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Commentary

Neuroprotection: at what cost, at what time, at what price?

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Abstract: Stroke and its disability have deserved the notoriety of a severe and potentially lethal condition, whose treatment is still challenging. The widely craved result of saving as much as possible from the neural tissue and eventually reviving what is thought to be in the ischemic penumbra – if not already dead and gone – is the outcome every clinician is dreaming of. There are several reviews on the issue, which have discussed several options of achieving neuroprotection in acute ischemic stroke. Of course, reviews are not and do not pretend to be exhaustive; new drugs enter repeatedly in the scene. We would limit our comments on some of the pharmacological agents, that although seem to be worldwide available, are still looking for obtaining the citizenship in the therapeutic armamentarium of acute ischemic stroke.

Keywords: Stroke, Neuroprotection, Edaravone, 3-N-Butylphthalide, Nerinetide

1. Introduction

A methodological clarification should be done right at the start, since the final outcome while treating a stroke patient, needs some quantification. Several scales of invalidity and morbidity are available. While talking about neuroprotection in acute (again: acute) stroke, it is clearly we are aiming to decrease the width of neural tissue injury. Yet the target group (patient demographics) is very inhomogeneous. Comorbidities are numerous and diverse. Use of other pharmacological agents is abundant and not without implications. Hence the need for a strong experimental basis to measure the efficacy of a potential neuroprotective agent. Let alone the fact that translation of experimental data into their proven effects on humans is a complicated road map, with ethical and skeptical deterrents.

2. Methodology

We have selected three chemical names of some relatively unknown preparations, considered as *neuroprotectants and neuroprotective therapy* and searched on PubMed with the combination of terms "name of the drug" and "stroke". The search was made based on the most recent papers (until the date 26 August 2024), and five most recent papers for each from the following drugs were included:

3-N-Butylphthalide (total mentions: 524 articles)

Edaravone dexborneol (total mentions: 39 articles)

Nerinetide (total mentions: 45 articles)

Large group of agents (for example, potential therapeutic agents targeting NVU) were not part of this commentary. Other potentially active drugs in this field include Sevoflurane *(>11600 articles)*, a well-known anesthetic. Also, substance P *(>26000 articles)* has been largely studied in the field of neurotransmission and pain and these two agents

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were not part of our commentary. Ferrostatin-1 (total mentions: *1024 articles*) and Clormethiazole (clomethiazole: *974 articles*) were also not part of this commentary, for their scope of pharmacological activity is much more wide than merely ischemic stroke. A pioneering paper of Lancet (2020) quoted from a recent source was as well mentioned in the references here below.

3. Results

Table 1. 3-N-Butylphthalide

Authors	Title	Citation	Core tip / conclusive remarks
Zhou H, Li S, Huang C, Chen Y, Wang L, Lin J, Lv Y.	A Preliminary Finding: N-butyl-phthalide Plays a Neuroprotective Role by Blocking the TLR4/HMGB1 Pathway and Improves Mild Cognitive Impairment Induced by Acute Cerebral Infarction.	J Integr Neurosci. 2024 Aug 21; 23(8):158.	NBP plays a neuroprotective role by inhibiting the TLR4/HMGB1 pathway and ameliorating ACI-induced MCI.
Cui Y, Hu Z, Wang L, Zhu B, Deng L, Zhang H, Wang X.	DL-3-n-Butylphthalide Ameliorates Post-stroke Emotional Disorders by Suppressing Neuroinflammation and PANoptosis.	Neurochem Res. 2024 Aug; 49(8):2215-2227.	NBP inhibited the toll-like receptor 4/nuclear factor kappa B signaling pathway, decreased the level of pro-inflammatory cytokines, including tumor necrosis factor-α, interleukin-1β, and M1-type microglia markers (CD68, inducible nitric oxide synthase), and reduced the expression of PANoptosis-related molecules including **caspase-1, caspase-3, caspase-8,** gasdermin D, and mixed lineage kinase domain-like protein in the hippocampus of the MACO rats.
Ge M, Jin L, Cui C, Han Y, Li H, Gao X, Li G, Yu H, Zhang B.	Dl-3-n-butylphthalide improves stroke outcomes after focal ischemic stroke in mouse model by inhibiting the pyroptosis-regulated cell death and ameliorating neuroinflammation.	Eur J Pharmacol. 2024 Jul 5; 974:176593.	NBP treatment significantly attenuates ischemic brain damage and promotes recovery of neurological function in the early and recovery phases after IS, probably by negatively regulating the **pyroptosis cell death** of neuronal cells and inhibiting toxic neuroinflammation in the central nervous system.
Zhu T, Dong S, Qin N, Liu R, Shi L, Wan Q.	Dl-3-n-butylphthalide attenuates cerebral ischemia/reperfusion injury in mice through AMPK-mediated mitochondrial fusion.	Front Pharmacol. 2024 Feb 22; 15:1357953.	NBP has the ability to modulate **mitochondrial homeostasis** by activating AMPK, leading to the mitigation of cerebral I/R injury. Importantly, our study presents novel evidence that the administration of NBP can effectively decrease infarct volume and enhance neurological functions by facilitating AMPK-mediated mitochondrial fusion in *in vivo* models of ischemic stroke.
Jiang Z, Wei J, Liang J, Huang W, Ouyang F, Chen C, Li P, Cao S, Cai Y, Li J, Huang B, Zeng J, Chen Y.	Dl-3-n-Butylphthalide Alleviates Secondary Brain Damage and Improves Working Memory After Stroke in Cynomolgus Monkeys.	Stroke. 2024 Mar; 55(3):725-734.	NBP improves working memory by alleviating remote secondary neurodegeneration and **neuroinflammation** in the ipsilateral dorsal lateral prefrontal cortex and thalamus after MCAO in cynomolgus monkeys.

Toxic neuroinflammation, mitochondrial homeostasis and caspase pathways are among the mentioned mechanisms [2-4]. Zhou et al had a study group of eighty-six patients [2]. The other studies mentioned in the Table 1 above, were all conducted with mice and monkeys.

Table 2. Edaravone dexborneol

Authors	Title	Citation	Core tip / conclusive remarks
Chen W, Zhang H, Li Z, Deng Q, Wang M, Chen Y, Zhang Y.	Effects of edaravone dexborneol on functional outcome and inflammatory response in patients with acute ischemic stroke.	BMC Neurol. 2024 Jun 20; 24(1):209.	Treatment with edaravone dexborneol resulted in a favorable functional outcome at 90 days post-stroke onset when compared to patients without this intervention; it also suppressed proinflammatory factors expression while increasing **anti-inflammatory** factors levels.
Xiao P, Huang H, Zhao H, Liu R, Sun Z, Liu Y, Chen N, Zhang Z.	Edaravone dexborneol protects against cerebral ischemia/reperfusion-induced blood-brain barrier damage by inhibiting ferroptosis via activation of nrf-2/HO-1/GPX4 signaling.	Free Radic Biol Med. 2024 May 1; 217:116-125.	This study revealed for the first time that Eda.B safeguarded the BBB from cerebral I/R injury by inhibiting **ferroptosis** through the activation of the Nrf-2/HO-1/GPX4 axis, providing a novel insight into the neuroprotective effect of Eda.B in cerebral I/R.
Wang C, Gu HQ, Dong Q, Xu A, Wang N, Yang Y, Wang F, Wang Y.	Rationale and design of Treatment of Acute Ischaemic Stroke with Edaravone Dexborneol II (TASTE-2): a multicentre randomized controlled trial.	Stroke Vasc Neurol. 2024 Mar 11: svn-2023-002938.	Edaravone, approved to treat amyotrophic lateral sclerosis by the US Food and Drug Administration, has proven to be cytoprotective through early **scavenging of free radicals** and later exerting anti-inflammatory effects to promote functional recovery and structural integrity in reperfusion animal models.
Wang D, Wang Y, Shi J, Jiang W, Huang W, Chen K, Wang X, Zhang G, Li Y, Cao C, Lee KY, Lin L.	Edaravone dexborneol alleviates ischemic injury and neuroinflammation by modulating microglial and astrocyte polarization while inhibiting leukocyte infiltration.	Int Immunopharmacol. 2024 Mar 30; 130:111700.	EDB protects against ischemic stroke injury by inhibiting the proinflammatory activation of microglia/macrophages and astrocytes and through reduction by invasion of circulating immune cells, which **reduces central and peripheral inflammation** following stroke.
Li J, Cao W, Zhao F, Jin P.	Cost-effectiveness of edaravone dexborneol versus dl-3-n-butylphthalide for the treatment of acute ischemic stroke: a Chinese health care perspective.	BMC Public Health. 2024 Feb 12; 24(1):436.	Edaravone dexborneol and dl-3-n-butylphthalide are two innovative brain **cytoprotective** drugs from China that have been approved and widely prescribed for acute ischemic stroke. Edaravone dexborneol is a cost-effective alternative compared with dl-3-n-butylphthalide for acute ischemic stroke patients in current medical setting of China.

Scavenging of free radicals, anti-inflammatory properties and cytoprotection after all, are among the mechanisms reputed to edaravone [7-11]. There is an ongoing large scale and multi-center trial (**TASTE-2**), that will enhance optimism to this preparation [9].

Table 3. Nerinetide

Authors	Title	Citation	Core tip / conclusive remarks
Tanaka K, Brown S, Goyal M, Menon BK, Campbell BCV, Mitchell PJ, Jovin TG, Saver JL, Muir KW, White PM, Bracard S, Guillemin F, Roos YBWEM, van Zwam WH, Najm M, Dowlatshahi D, Hill MD, Demchuk AM; HERMES Collaborators.	HERMES-24 Score Derivation and Validation for Simple and Robust Outcome Prediction After Large Vessel Occlusion Treatment.	Stroke. 2024 Aug; 55(8):1982-1990.	The post-treatment HERMES-24 score is a simple validated score that predicts a 3-month outcome after anterior circulation large vessel occlusion stroke regardless of intervention, which helps prognostic discussion with families on day 2.
Siddiqi AZ, Kashani N, Dmytriw AA, Yavagal DR, Saposnik G, Tymianski M, Adams C, Hill MD, Dowlatshahi D, Katsanos AH, Menon BK, Ganesh A, Singh N.	Cytoprotective agents in stroke: Still uncertainty in the next frontier.	J Stroke Cerebrovasc Dis. 2024 Sep; 33(9):107860.	Pharmacologic interactions result in major **uncertainty** about cytoprotective treatment choices.
Dammavalam V, Lin S, Nessa S, Daksla N, Stefanowski K, Costa A, Bergese S.	Neuroprotection during Thrombectomy for Acute Ischemic Stroke: A Review of Future Therapies.	Int J Mol Sci. 2024 Jan 10; 25(2):891.	Advances in multiple neuroprotective therapies, including uric acid, activated protein C, **nerinetide**, otaplimastat, imatinib, verapamil, butylphthalide, edaravone, nelonemdaz, ApTOLL, regional hypothermia, remote ischemic conditioning, normobaric oxygen, and especially nuclear factor erythroid 2-related factor 2, have promising evidence for improving stroke care.
Kim H, Choi S, Kim DE.	Preclinical Replication Study of the Postsynaptic Density Protein-95 Inhibitor Nerinetide.	J Clin Neurol. 2024 May; 20(3):330-332.	The present study does suggest that implementing **multicenter animal studies** is warranted to enhance the reproducibility and generalizability of preclinical observations.
Hill MD, Goyal M, Menon BK, Nogueira RG, McTaggart RA, Demchuk AM, Poppe AY, Buck BH, Field TS, et al; ESCAPE-NA1 Investigators.	Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (**ESCAPE-NA1**): a multicentre, double blind, randomized controlled trial.	Lancet. 2020 Mar 14; 395(10227):878-887.	Nerinetide, an eicosapeptide that interferes with post-synaptic density protein 95, is a neuroprotectant that is effective in **preclinical stroke models of ischemia-reperfusion.** Nerinetide did not improve the proportion of patients achieving good clinical outcomes after endovascular thrombectomy compared with patients receiving placebo.

There are also several studies on nerinetide, and its potential benefits on ischemic stroke; ESCAPE-NA1 presented the initial results on 2020 but still guidelines are needed [12-16].

Regarding the same drug, reviews are available, still raising uncertainties while promoting optimism [13, 14].

4. Remarks

There is an obvious need towards the optimization of clinical trial protocols [1]. The first two neuroprotectants that are mentioned here above come out mostly or exclusively from Chinese authors and sources; hence the need for raising awareness in other settings.

Their use in the next future (namely of N-butyl-phthalide and edaravone) is beyond all doubts, of great interest to clinicians treating stroke and cerebral ischemia.

Obviously, it is hard to extrapolate pre-clinical studies (experimental; animal data) into plausible, convincing clinical outcomes [17, 18]. As a source pointed out, successful bench-to-bedside translations are still lacking [18]. Nevertheless, expert opinions are still of high value, and might guide individual patients' treatment; provided safety and familiarity with certain drug(s) is ensured. A question of time more than a question of economy and availability, obviously.

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