Viewpoint

Cholinergic deregulation in intracerebral haemorrhage: an insight

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Intracerebral haemorrhage (ICH) accounts for 10–15% of all strokes. Despite high incidence, morbidity and mortality, the pathophysiology of ICH remains unclear. During the last decade new experimental and clinical data has been revealed shedding more light on the fact that ICH is characterized by two main phases: (I) the 'initial injury', which means the haematoma onset, described as 'primary injury' and characterized mainly by the mass effect of the haematoma in the surrounding brain parenchyma; and (II) the 'secondary injury', as a result of the events following the initial bleed. The 'secondary injury' implicates a number of different molecular pathways leading to the development of cytotoxicity, excitotoxicity, hypermetabolism, oxidative stress, and inflammation. The final result of all these parallel pathways being activated is blood brain barrier disruption, oedema and neuronal cell death. During this injurious and complex neurometabolic process, the local response to the clot, generates inflammatory response, in which microglia and macrophages play a key role. The role of the cholinergic system is one of the less studied aspects of the ICH-inducing neuroinflammatory responses.

Our current knowledge regarding the role of the cholinergic system in several pathologies of the central nervous system is limited. There is evidence that apart from its well-known role in neurotransmission, the cholinergic system is also important in brain injury and recovery, affecting several neuroinflammatory pathways (1,2) in many brain pathologies. Recent data suggests that in addition to the known role of the cholinergic system in neurodegenerative disorders, the acetylcholine-mediated system of neurotransmission also plays an important role in traumatic brain injury (TBI); in fact, experimental studies in murine TBI models have already revealed an implication of the expression of alpha7 nicotinic cholinergic receptor (α7nAChR) in TBI pathophysiology (3).

However, very few experimental and clinical studies so far have attempted to study the role of the cholinergic system in the ICH pathology. The first of these studies dates back as early as in 1972, while more than three decades later, Garibova *et al.* (4), observed in a rat model of haemorrhagic stroke with cholinergic deficit, that memantine administration (a low-affinity non-competitive antagonist of glutamatergic NMDA-subtype receptors), resulted on complete elimination of the ICH-induced animals loss, reduced the final neurological deficit, improved the conditioned passive avoidance reflex and decreased the emotional stress. About the same time, Ohnishi *et al.* (5) showed that a long-term treatment with nicotine could partially prevent the thrombin-induced neuron loss in cortico-striatal slice cultures and could suppress the thrombin-induced increase in activated microglia; *in vitro* findings that suggested a novel action of nicotine on neural tissues. Similarly, Hijioka *et al.* (6) have undertaken an extensive study of the therapeutic effect of nicotine on a mouse model of ICH; they used a collagenase mouse model of ICH (induced by intrastriatal injection) and they performed a daily intraperitoneal administration of nicotine starting 3 hours after the haematoma induction, resulting in inhibition of apoptosis, decreased the number of striatal neuronal loss 3 days after the onset, attenuated the activation of microglia/macrophages and neutrophil infiltration, without affecting haematoma expansion and brain oedema. The outcome of nicotine administration was improved sensorimotor performance and survival rate (6). Furthermore, studying whether subtype-specific agonists of nicotinic acetylcholine receptors, could preserve tissue integrity in a mouse model of ICH *in vivo* (7), daily intraperitoneal administration of PNU-282987 (an

α7nAchR receptor agonist), increased the final number of neurons that survived at and around the haematoma area 3 days after the haematoma induction and decreased the number of activated microglia/macrophages in the perihaematomal region. On the other hand, the number of microglia/macrophages in the central region of hematoma at the early phase of pathology (6 hours after the ICH induction) increased after PNU-282987 administration (7). The latter finding suggests that α7nAChR agonists could provide a neuroprotective effect on ICH-induced injury, independently of their anti-inflammatory actions (7).

In similar to the above studies, Krafft *et al.* (1,2) have shown firstly that α7nAChR stimulation improves functional and morphological outcomes after ICH induction in mice as well as that PHA-543613 (a novel α7nAChR agonist) preserves blood-brain barrier integrity. It is worth noting that PHA-543613 was also found to reduce the expression of pro-apoptotic GSK-3β through the PI3K-Akt signaling pathway, and that it is well-established that the cholinergic system, is involved in the inflammatory process of 'secondary injury' after the haematoma formation.

Duris *et al.* (8), reviewing the cholinergic anti-inflammatory pathway (CHAIP) in both haemorrhagic and ischaemic stroke, suggested that CHAIP, is a mechanism by which central nervous system regulates immune response and controls inflammation. According to the authors (8), targeting CHAIP in cases of haemorrhagic and ischaemic stroke, either with pharmacological stimulation of α7nAChR or via vagus nerve stimulation (VNS), could result in immunomodulation without immunosuppression.

Finally, in an experimental study of hours (9), in the autologous blood injection porcine model of ICH used, an activation of acetylcholinesterase (AChE; a crucial membrane enzyme involved in cholinergic neurotransmission) was observed 24 h after U-74389G (a lazaroid antioxidant) administration; a finding that suggests a possible neuroprotective role of the lazaroid, given that after brain injury, reduced AChE activity is expected (9).

The available data suggest that in ICH, immediately after the bleeding and clot formation, CHAIP is activated providing a physiological mechanism by which the central nervous system regulates immune response and controls inflammation. The performance of VNS (tested in animal models of chronic tinnitus, ischemic stroke, ICH, TBI and post-traumatic stress disorder) seems promising and pilot clinical studies in patients with neurological disorders, have demonstrated that VNS supports plasticity and facilitates the effects of neurorehabilitation when applied an adjunctive strategy in these cases. On the other hand, pharmacological stimulation of α7nAChR seems to be another important target of neuroprotection (10).

The above-mentioned studies of the role of the cholinergic system in ICH fail to provide critical information about the patent of its modulation in ICH. The time-depended response of the cholinergic system, its early role in ICH (and other pathologies), as well as the pathways triggered and involved, need further investigation. For example, the involvement of the cholinergic system could explain the reduced consciousness of ICH patients, even in cases with small bleeds and/or a minimal mass effect of the haematoma.

The importance of the cholinergic system in ICH is far more complex that the currently available experimental and clinical data implies, while the limited data available could be due to the difficulty in scheduling experiments regarding the cholinergic system deregulation in ICH and/or or an underestimation of the importance (in both clinical and experimental studies) of the multiple roles of the system. The efficacy of nicotine or α7nAChR agonists (such as PHA-543613, PNU-282987) administration as a neuroprotective approach in ICH requires further investigation and should be primarily applied in the early stages of ICH. The same applies to VNS.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Krafft PR, Altay O, Rolland WB, et al. α7 nicotinic acetylcholine receptor agonism confers neuroprotection through GSK-3β inhibition in a mouse model of intracerebral hemorrhage. Stroke 2012;43:844-50.
2. Krafft PR, Caner B, Klebe D, et al. PHA-543613 preserves blood-brain barrier integrity after intracerebral hemorrhage in mice. Stroke 2013;44:1743-7.
3. Bimpis A, Baillie GS, Zarros A. Cholinergic deregulation in traumatic brain injury could be a pathophysiology-related biphasic epiphenomenon. Med J Malaysia 2014;69:148.

4. Garibova TL, Voronina TA, Litvinova SA, et al. Features of memantine action profile in cholinergic deficit and intracerebral posttraumatic hematoma (hemorrhagic stroke) models in rats. Eksp Klin Farmakol 2008;71:8-13.
5. Ohnishi M, Katsuki H, Takagi M, et al. Long-term treatment with nicotine suppresses neurotoxicity of, and microglial activation by, thrombin in cortico-striatal slice cultures. Eur J Pharmacol 2009;602:288-93.
6. Hijioka M, Matsushita H, Hisatsune A, et al. Therapeutic effect of nicotine in a mouse model of intracerebral hemorrhage. J Pharmacol Exp Ther 2011;338:741-9.
7. Hijioka M, Matsushita H, Ishibashi H, et al. α7 Nicotinic acetylcholine receptor agonist attenuates neuropathological changes associated with intracerebral hemorrhage in mice. Neuroscience 2012;222:10-9.
8. Duris K, Lipkova J, Jurajda M. Cholinergic Anti-inflammatory Pathway and Stroke. Curr Drug Deliv 2017;14:449-57.
9. Bimpis A, Papalois A, Tsakiris S, et al. Activation of acetylcholinesterase after U-74389G administration in a porcine model of intracerebral hemorrhage. Metab Brain Dis 2012;27:221-5.
10. Sussman ES, Kellner CP, McDowell MM, et al. Alpha-7 nicotinic acetylcholine receptor agonists in intracerebral hemorrhage: an evaluation of the current evidence for a novel therapeutic agent. Neurosurg Focus 2013;34:E10.

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