LETTER TO EDITOR

Cholinergic deregulation in traumatic brain injury could be a pathophysiology-related biphasic epiphenomenon

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Dear Editor

Samuel and Ng have recently provided an interesting and well-researched case report on the beneficial use of donepezil in a case of traumatic brain injury (TBI)[1]. The authors suggest that *"anticholinergic agents may benefit patients with moderate TBI… even if therapy is started late in the course of the treatment"*[1]. Despite the patient's old age (75-years-old), a criterion that might exert some doubt over the fact that donepezil administration would benefit any age-matched individual under the specific treatment scheme, the demonstrated memory and behavior improvement is significant[1] and there is recent clinical evidence of the beneficial effect of donepezil on cognitive function and cerebral cortical metabolism in TBI patients (as compared to suitably-selected control subjects)[2].

Interestingly, recent experimental studies have provided evidence of a significant time-dependent and brain-region-specific deregulation of the cholinergic system during the early phases of TBI pathophysiology, involving: (i) changes in acetylcholinesterase (AChE) activity[3,4], (ii) down-regulation of the alpha-7 nicotinic acetylcholine receptor (α7 nAChR)[5], as well as (iii) reduction of the vesicular acetylcholine transporter (vAChT) and muscarinic acetylcholine receptor (mAChR) levels[6]. These data are of significant value, as our knowledge regarding the cholinergic response during the early phases of TBI pathophysiology in humans is limited[7]. What we know for sure is that there seems to be an early, post-injury cholinergic excess in terms of the measured cerebrospinal fluid acetylcholine levels (non-specific, as it is accompanied by a generalized neurotransmitter excess)[7], followed by well-established late-phase cortical cholinergic deficits[7,8]. However, is this biphasic deregulation directly related to the TBI pathophysiology and to what extent could it be exploited therapeutically?

It is our opinion that (and as the title suggests), the cholinergic deregulation observed in TBI is probably a biphasic, pathophysiology-related epiphenomenon (a consequence and a non-specific component of the natural history of TBI). During early post-injury phase, dynamic changes occur in the brain causing metabolic, inflammatory and re-adaptational changes, which affect all systems of neurotransmission and that are region-specific, time-dependent and different among the different types of TBI. Although there is significant evidence for the involvement of the cholinergic system in the control of neuroinflammation[5,9], these dynamic changes seem to affect the cholinergic system to an equal extent compared with other systems of neurotransmission, and unless they result in serious cerebral cholinergic neuronal injury or ascending cholinergic fiber loss[7], will provide TBI survivors with significant post-traumatic cholinergic deficits. Within this context, as well as in other serious brain diseases such as intracerebral haemorrhage[10,11], a systematic effort should be undertaken to clarify the effect of any potential limitation of the early post-injury cholinergic excess in terms of survival, neuronal injury and long-term cognitive recovery, as well as to shed more light on the role of AChE (a major neuropharmacological target) in the early phase of TBI's natural history in humans. This might allow for the beneficial use of cholinomimetic compounds in the earlier (dynamically-evolving) stages of TBI.

REFERENCES

1. Samuel GS, Ng YS. A case report on the use of an acetylcholinesterase inhibitor (donepezil) in traumatic brain injury. Med J Malaysia 2013; 68(4): 376-378.
2. Kim YW, Kim DY, Shin JC, Park CI, Lee JD. The changes of cortical metabolism associated with the clinical response to donepezil therapy in traumatic brain injury. Clin Neuropharmacol 2009; 32(2): 63-68.
3. Donat CK, Schuhmann MU, Voigt C, Nieber K, Schliebs R, Brust P. Alterations of acetylcholinesterase activity after traumatic brain injury in rats. Brain Inj 2007; 21(10): 1031-1037.
4. Valiyaveettil M, Alamneh YA, Miller SA, Hammamieh R, Arun P, Wang Y, Wei Y, Oguntayo S, Long JB, Nambiar MP. Modulation of cholinergic pathways and inflammatory mediators in blast-induced traumatic brain injury. Chem Biol Interact 2013; 203(1): 371-375.
5. Kelso ML, Oestreich JH. Traumatic brain injury: central and peripheral role of alpha7 nicotinic acetylcholine receptors. Curr Drug Targets 2012; 13(5): 631-636.
6. Donat CK, Schuhmann MU, Voigt C, Nieber K, Deuther-Conrad W, Brust P. Time-dependent alterations of cholinergic markers after experimental traumatic brain injury. Brain Res 2008; 1246: 167-177.
7. Arciniegas DB. Cholinergic dysfunction and cognitive impairment after traumatic brain injury. Part 2: evidence from basic and clinical investigations. J Head Trauma Rehabil 2011; 26(4): 319-323.
8. Östberg A, Virta J, Rinne JO, Oikonen V, Luoto P, Någren K, Arponen E, Tenovuo O. Cholinergic dysfunction after traumatic brain injury: preliminary findings from a PET study. Neurology 2011; 76(12): 1046-1050.
9. Wessler I, Kirkpatrick CJ. Acetylcholine beyond neurons: the non-neuronal cholinergic system in humans. Br J Pharmacol 2008; 154(8): 1558-1571.
10. Hijioka M, Matsushita H, Hisatsune A, Isohama Y, Katsuki H. Therapeutic effect of nicotine in a mouse model of intracerebral hemorrhage. J Pharmacol Exp Ther 2011; 338(3): 741-749.
11. Bimpis A, Papalois A, Tsakiris S, Zarros A, Kalafatakis K, Botis J, Stolakis V, Zissis KM, Liapi C. Activation of acetylcholinesterase after U-74389G administration in a porcine model of intracerebral hemorrhage. Metab Brain Dis 2012; 27(2): 221-225.

This article was accepted: 4 April 2014
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