Letter by Macrez et al Regarding Article, “Preexisting Serum Autoantibodies Against the NMDAR Subunit NR1 Modulate Evolution of Lesion Size in Acute Ischemic Stroke”

To the Editor:

The recent article by Zerche et al. shows that circulating N-methyl-D-aspartate-receptor subunit NR1 (NMDAR)-GluN1 autoantibodies modulate the evolution of lesion size in ischemic stroke patients.1 We think that mechanistic explanations of these exciting data could be found in previous papers published in Stroke by our group.2,3 In these papers, we showed that vaccination against the N-terminal domain of the GluN1 subunit of NMDA receptors reduces lesion size in mouse experimental stroke by preventing blood–brain barrier (BBB) breakdown.

Zerche et al. report that circulating NMDAR-GluN1 autoantibodies reduce stroke lesions only in patients with intact BBB before stroke (apolipoprotein E4 [APOE4] noncarriers), but not in patients with a preexisting BBB leakage (APOE4 carriers). A possible interpretation of these data, in light of our previous reports, would be that NMDAR-GluN1 autoantibodies protect APOE4 noncarrier patients from BBB leakage, but fail to do so in APOE4 carriers, in which the BBB is already leaky before stroke, leaving less opportunity for BBB protection.

The question of how NMDAR-GluN1 antibodies can protect BBB is intriguing. In fact, part of the answer is given by the demonstration of the expression of NMDAR on brain endothelial cells, and their involvement in leukocyte diapedesis through endothelial cells—a process linked to BBB leakage. Additional explanation resides in the evidence of a link between NMDA receptors and tissue-type plasminogen activator (tPA; Actilyse), which plays a central role in BBB breakdown in animal models of stroke. Noteworthy, tPA enhances NMDAR function by interacting with GluN1. Based on these data, we postulated that immunizing mice against NMDAR-GluN1 would block tPA/NMDAR interactions and provide a protective effect. Indeed, active or passive immunization against the N-terminal domain of GluN1 reduced ischemic lesions, improved neuroscore, and, in relevance to the topic of this letter, reduced BBB leakage. Interestingly, we showed that the antibodies responsible for this protective effect block the action of tPA on the GluN1 subunit. In line with this, we recently developed a monoclonal antibody directed against the site of interaction of tPA with NMDAR-GluN1, in the framework of a patent orientated toward the treatment of neurological disorders, such as stroke (patent no EP 2473185-A1-20120711).

A crucial question would then be to determine whether part of the NMDAR-GluN1 autoantibodies found in patients recognize the binding site of tPA on GluN1 and, thus, modulate their interaction. This could bring important advances toward the explanation of the mechanism by which NMDAR-GluN1 antibodies provide protection in stroke patients.

To conclude, we want to highlight the astonishing concordance between the data presented in Zerche et al.’s paper in human, with the results previously published by our group from animal studies. These different studies agree to say that circulating NMDAR-GluN1 antibodies protect the brain after stroke, in relation to BBB leakage. We are convinced that these data bring hope for the use of antibodies preventing the interaction of tPA with NMDAR, alone or in combination with tPA, for the treatment of stroke patients.

Disclosures

None.

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