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 in 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 studies. These different studies agree to say that circulating AR-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.

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.

Richard Macrez, PhD

Denis Vivien, PhD

Fabian Docagne, PhD

Inserm, Inserm UMR-S U919

Serine Protease and Pathophysiology of the Neurovascular Unit

GIP Cyceron, University of Caen Lower-Normandy

Caen, France


Letter by Macrez et al Regarding Article, "Preexisting Serum Autoantibodies Against the NMDAR Subunit NR1 Modulate Evolution of Lesion Size in Acute Ischemic Stroke"
Richard Macrez, Denis Vivien and Fabian Docagne

*Stroke*, published online May 28, 2015;
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/05/28/STROKEAHA.115.009670.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/