Response to Letter Regarding Article, “Preexisting Serum Autoantibodies Against the NMDAR Subunit NR1 Modulate Evolution of Lesion Size in Acute Ischemic Stroke”

We thank Richard Macrez and colleagues for writing this complementary letter regarding our recent article.1 The letter nicely extends the discussion on possible mechanisms of action that might contribute to the consequences of preexisting N-methyl-D-aspartate-receptor subunit NR1 (NMDAR1) autoantibodies (AB) on brain functions. We agree that the role of endothelial NMDAR1 in blood–brain barrier (BBB) permeability and monocyte transmigration is intriguing. Also, the fact that in our study the modulating effects of NMDAR1-AB were less prominent in r-tPA (recombinant tissue-type plasminogen activator) as compared with non-r-tPA treated patients, despite their higher N number (see Figure IV),1 may support an additional modifier influence of (exogenous) r-tPA on outcome that is probably independent of its thrombolytic activity. BBB integrity before stroke, however, at least tended to have the same influence regardless of r-tPA treatment: Beneficial NMDAR1-AB effects in individuals with previously intact BBB but harmful effects in APOE4 carriers with leaky BBB before the ischemic insult.

Nevertheless, beyond a potentially important role of the cerebrovascular endothelium, we have to consider that other cell types in the brain likely contribute to short-term and long-term outcome after stroke. Also cells of the oligodendrocyte lineage and astrocytes are known to express NMDAR1, which may influence their neuron/axon supporting, detoxifying, metabolic, protection, or defense properties.2–4 Blocking these NMDAR1 functions by AB may ultimately codetermine stroke outcome. In fact, antagonizing NMDAR1 not only on neurons and endothelial cells but also on glia by NMDAR1-AB in the event of a sudden BBB breakdown versus a subtle-permanent BBB leakage might variably contribute to the modulation of brain functions. Importantly, in conditions of hypoxia/ischemia, inflammation or demyelination but also during normal development and perhaps even intensive learning processes, NMDAR1 expression may be significantly increased and thus effects of AB binding be more prominent.2–4

In conclusion, much more work will have to go into understanding consequences of circulating NMDAR1-AB in disease states with accompanying BBB breakdown, where these AB may possibly play the role of a double-edged sword. Reduction of lesion size during acute ischemia may be followed by an increased risk of cognitive decline, epilepsy, or psychosis on extended AB exposure of the brain because of a lastingly compromised BBB after stroke.1 Further studies will be necessary to evaluate potential benefits of passive (rather than active) immunization under carefully controlled conditions.

Disclosures

None.

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