contrast, excitatory synaptic transmission in CA1 region of rat hippocampus depends on three kinds of excitatory amino acid receptors: quisqualate, kainate, and N-methyl-D-aspartate (NMDA) receptors (see, e.g., [5]). Nevertheless, a common underlying mechanism could still be feasible, involvement of different transmitter systems notwithstanding. Indeed, De Deyn and Macdonald [1] suggested the blocking of the GABA and glycine receptor–associated ion channel as the cause of guanidino compound GABA and glycine antagonism. GSA could disturb the function of excitatory amino acid receptors in rat hippocampus in a similar fashion. Thus, blockage of receptor associated ion channels could be a candidate common mechanism. Certainly, further work will be needed to test this hypothesis.

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Reply

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D'Hooge and colleagues have demonstrated that guanidinosuccinic acid (GSA) disrupts excitatory synaptic transmission between Schaffer collateral axons and CA1 hippocampal pyramidal cells in the rat hippocampal slice. These results complement our observation that GSA reduces GABAergic inhibition and suggest that GSA may have multiple effects on neurotransmitter receptor systems. Further investigation of the interactions of these metabolites with neurotransmitter systems may clarify the bases for the neurological deficits seen in uremic encephalopathy.

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T-cell Receptor Biology and Multiple Sclerosis

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In their recent paper on the V_β-gene usage in multiple sclerosis (MS) patients [1], Lee and coworkers interpreted their interesting findings of oligoclonal T cells and of "recurrent" T-cell receptor (TcR) idiotypes as indicative of the operation of a specific antigen, probably located in the myelin sheath. Knowledge of clonality and idiotypic interactions is much more limited for the TcR than for immunoglobulins (Ig). This justifies drawing analogies between the two arms of the immune system.

On the humoral level, restricted heterogeneity resulting in an "oligoclonal IgG pattern" is, in fact, characteristic of specific immune responses to defined infectious agents like mumps virus, herpes simplex virus, and subacute sclerosing panencephalitis virus. It is also a main characteristic of early, germ-line encoded "natural" antibodies [2, 3], the typical features of which are multispecificity toward foreign and self-antigens, low avidity to the different antigens, and a high degree of idiotypic interconnectivity possibly allowing self-aggregation [4, 5]. Recurrent or "public" Ig idiotypes are found predominantly on antibodies directed against highly conserved autoantigens (e.g., DNA, Ig, MHC products, cytoskeletal proteins, and so on) [6], and these are also the main targets of natural antibodies [4, 5].

Assuming analogies between Ig and TcR, the findings of Lee and associates [1] might be compatible with the activation of some type of "natural" T cells having more immunoregulatory properties than being specifically targeted against a defined (myelin) autoantigen and thus a typical part of a mature immune response.

The occurrence of natural antibodies [7] and elevated numbers of CD5+ B cells (the probable source of natural antibodies) [8] in the CSF of MS patients might indicate regression of the intrathecal immune system to an immature state that normally characterizes only fetal and neontal life [3–5] and lower vertebrates [2]. The heterogeneity of the intrathecal antibody response with respect to antigen specificities [9], along with the low avidity of such antibodies [10] and the lack of any reactivity with a number of viruses and MBP by the oligoclonal T cells reported by Lee and colleagues [1], is in line with this interpretation. When assuming an important immunoregulatory role of such putative "natural" T cells in the CNS of MS patients, the search for anti-HLA-class 2 activity of these clones, as demonstrated, for example, in the autologous mixed lymphocyte reaction, might be an interesting tool, all the more because an anti-Ia T-cell response resulted in a polyclonal activation in vitro [11], and evidence of polyclonal background B-cell activation exists in MS [9].

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