Dual inhibition of proteasomal and lysosomal proteolysis ameliorates autoimmune central nervous system inflammation

Nicolas Fissolo, Marianne Kraus, Michael Reich, Miriam Ayturan, Herman Overkleeft, Christoph Driessen & Robert Weissert

Multiple sclerosis (MS) is a detrimental disease of the central nervous system (CNS) leading to long-term disability. In the course of animal models of multiple sclerosis (experimental autoimmune encephalomyelitis), we find enhanced activity of proteasome subunits beta1i, beta2, beta2i and beta5 in the CNS. We demonstrate that pharmacological inhibition of the proteasome by bortezomib ameliorates experimental autoimmune encephalomyelitis in mice and rats in prophylactic and therapeutic treatment with reduced numbers of T-cells secreting proinflammatory cytokines. The anti-inflammatory effect of proteasome inhibition was accompanied by reduced NF-kappaB activity in the CNS and lymphoid organs. The combined inhibition of proteasomes and lysosomal proteases involved in major histocompatibility complex II antigen presentation further improved therapeutic efficacy. We suggest proteasome inhibition alone or in combination with inhibition of lysosomal proteases as a novel therapeutic strategy against inflammation-induced neurodegeneration in the CNS. We demonstrate the impact of the proteasome and lysosomal proteases on development of autoimmunity.