21.4.3 Neurodegenerative Diseases

Accumulating evidence indicates that histone acetylation plays a crucial role in the etiology of neurodegenerative disorders. Several recent studies have highlighted the importance of HDACs and modifications of histone acetylation in Alzheimer's disease,[85] neuronal memory, learning, synaptic plasticity and neural regeneration.[86] This is not surprising since neurodegenerative diseases such as amyotrophic lateral sclerosis, polyglutamine-related diseases, as well as Parkinson's and Alzheimer's disease are known to be accompanied by transcriptional dysfunctions, leading to neuronal death.[87]

HDACIs show great promise to combat ageing-associated neurodegenerative diseases[70,88–90] and to ameliorate the symptoms of cognitive decline, post-traumatic stress disorder and depression.[91] Some studies demonstrate that HDACIs may be neuroprotective by regulating memory and synaptic dysfunctions in both *in vitro* and *in vivo* models of this pathology.[85] HDACIs were also reported to cause beneficial effects in both *in vitro* and *in vivo* models of Parkinson's disease. For example, a HDAC1/2 isoform-specific inhibitor, K560, was recently found to protect against pharmacologically induced neuronal death and to mitigate experimental Parkinson's disease in both *in vitro* and *in vivo* models of this disease.[92] Other HDACIs, such as SAHA and SB, were shown to improve memory function in the mouse model of Alzheimer's disease.[93,94] The potential mechanisms underlying these effects include maintenance of histone acetylation homeostasis and transcriptional activation of neuronal survival genes.[95] In the last few years, clinical trials have been initiated to examine the effectiveness of HDACIs in patients with Parkinson's disease. The loss of functional activity of HATs is likely a common mechanism related to the impairment of the chromatin acetylation status throughout the lifetime of neurons. The therapeutic potential of HAT activators in the treatment of neurodegenerative disorders has been established in preclinical studies. Substantial neuroprotective properties were revealed for one of the HATs termed cAMP response element binding protein (CREB)-binding protein (CBP), and also for several other HATs that were shown to be essential for processes of neuronal plasticity and memory formation.[87]

21.4.4 Inflammatory Disorders

Non-specific HDACIs also demonstrated anti-inflammatory effects in both *in vitro* and *in vivo* models.[96,97] Recently, evidence was obtained for the role of the NF-κB signal transduction pathway in mediating the effects of HDACIs on inflammatory responses.[98] The important point is that such effects were reported at concentrations that were 10–100-fold lower than the concentrations required for the anti-cancer effects of these compounds. Clinical application of these substances for treating inflammatory diseases is, however, hampered due to their low specificity and a wide variety of HDACs that they affect throughout the body.[99]