Cyclic Adenosine Monophosphate (cAMP)-Induced Histone Hyperacetylation Contributes to its Antiproliferative and Differentiation-Inducing Activities

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Histone acetylation is linked to the control of chromatin remodeling, which is involved in cell growth, proliferation, and differentiation. It is not fully understood whether cyclic adenosine monophosphate (cAMP), a representative differentiation-inducing molecule, is able to modulate histone acetylation as part of its anticancer activity. In the present study, we aimed to address this issue using cell-permeable cAMP, *i.e.* dibutyryl cAMP (dbcAMP) and C6 glioma cells. As reported previously, under the conditions of our studies, treatment with dbcAMP clearly arrested C6 cell proliferation and altered their morphology. Its antiproliferative and differentiation-inducing activity in C6 glioma cells involved upregulation of $p21^{WAF/CIP}$, $p27^{kip1}$, glial fibrillary acidic protein (GFAP), and Cx43, as well as downregulation of vimentin. Furthermore, dbcAMP modulated the phosphorylation of ERK and Akt in a time-dependent manner and altered the colocalization pattern of phospho-Src and the actin cytoskeleton. Interestingly, dbcAMP upregulated the enzyme activity of histone acetyltransferase (HAT) and, in parallel, enhanced cellular acetyllysine levels. Finally, the hyperacetylation-inducing compound, sodium butyrate (NaB), a histone deacetylase (HDAC) inhibitor, displayed similar anticancer activity to dbcAMP. Therefore, our data suggest that antiproliferative and differentiation-inducing activities of dbcAMP may be generated by its enhanced hyperacetylation function.

Key words: Cyclic AMP, Antiproliferative Effect, Histone Acetylation