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National and Kapodistrian University
of Athens – Faculty of Chemistry

N.C.S.R. "Demokritos"
Institute of Physical Chemistry

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NMR study of Nickel binding to N-tail of Histone H4

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Nickel has been shown to be an essential trace element involved in the metabolism of several species of bacteria, archea, plant and may yet be found to play a role in the metabolism of higher organisms[1] . However, the carcinogenicity of certain nickel compounds has been confirmed by the combination of epidemiological evidence in humans and carcinogenesis bioassays in animals [2]. The molecular mechanisms of nickel-induced carcinogenesis include interactions of this metal with major chromatin components causing alterations in gene expression rather than by direct DNA damage. We have previously reported that nickel is a potent suppressor of histone H4 acetylation, in both yeast and mammalian cells [3-5]. It has preference to specific lysine residues in the N-terminal tail of histone H4, in which the sites of acetylation are clustered.
Here we present our recent results on the coordination ability of Ni(II) to the N-terminal tail of Histone H4 using NMR spectroscopy. A series of 1D, 2D Tocsy and Noesy ^{1}H NMR spectra of the tail with increasing nickel concentration to the final molar ratio 1:1, were acquired.

References

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NMR study of Nickel binding to N-tail of Histone H4

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The molecular mechanisms of nickel-induced carcinogenesis include interactions of this metal with major chromatin components causing alterations in gene expression rather than by direct DNA damage [1,2]. We have previously reported that nickel is a potent suppressor *in vivo* of histone H4 acetylation, in both yeast and mammalian cells [3]. Acetylation induces an increase in a-helical content in the histone tails of the nucleosome, particularly in the N-terminal domain of histone H4. It causes a shortening of the tail and, such effect, may have important structural and functional implication as a mechanism of transcriptional regulation. In our study we found that also nickel can cause conformational changes on the histone H4 protein and the same as acetylation it induces an increase in the a-helical conformation of the histone H4. In order to focus the conformational changes in the a-helical-inducted region and the role exhibit by the side-chain in the complex stability, the interactions between Ni(II) and the N-terminal region of histone H4, Ac-SGRGKGGKGLGKGGAKRHRKVLRDNIQGIT-Am, were studied using NMR spectroscopy. A series of 1D and 2D Tocsy and Noesy ^{1}H-NMR spectra of the peptide-ligand with increasing of nickel concentration to the final molar ratio 1:1, were acquired. The complex was studied at pH 9, a the maximum level 4N of metal coordination to the peptide, with respect the our potentiometric analysis previous reported [4,5].

References

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