Exploring the Conformational Space of Growth Hormone - Releasing Hormone Analogs using Dopant Assisted Trapped Ion Mobility Spectrometry – Mass Spectrometry

by Javier Moreno | Kevin Jeanne Dit Fouque | Francisco Fernandez-Lima

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Recently, we proposed a high-throughput screening workflow for the elucidation of agonistic or antagonistic growth hormone – releasing hormone (GHRH) potencies based on structural motif descriptors as a function of the starting solution. In the present work, we revisited the influence of solution and gas-phase GHRH molecular micro-environment using trapped ion mobility – mass spectrometry (TIMS-MS). The effect of the starting solvent composition (10 mM ammonium acetate (NH4Ac), 50% methanol (MeOH), 50% acetonitrile (MeCN) and 50% acetone (Ac)) and gas-phase modifiers (N2 , N2 +MeOH, N2 +MeCN and N2 +Ac) on the conformational states of three GHRH analogs, GHRH (1-29), MR-406 and MIA-602 is described as a function of the trapping time (100 – 500 ms). Changes in the mobility profiles were observed showing the dependence of the conformational states of GHRH analogs according to the molecular micro-environment in solution, suggesting the presence of solution memory effects on the gas-phase observed structures. The use of gas modifiers resulted in smaller mobilities, with a direct correlation between the size and mass of the organic modifier, and more importantly led to substantial changes in relative abundances of the IMS profiles. We attributed the observed changes in the mobility profiles by clustering of GHRH analog ions and the gas modifiers, re-defining the free energy landscape and leading to other local minima structures. Moreover, inspection of the mobility profiles as a function of the trapping time (100 to 500 ms) allowed for conformational inter-conversions toward more stable “gas-phase” structures. These experiments enabled us to outline a more detailed description of the structures and intermediates involved in the biological activity of GHRH, MR-406 and MIA-602.