The necessity of long-term molecular dynamics simulations: Deamino-oxytocin - novel conformational insights

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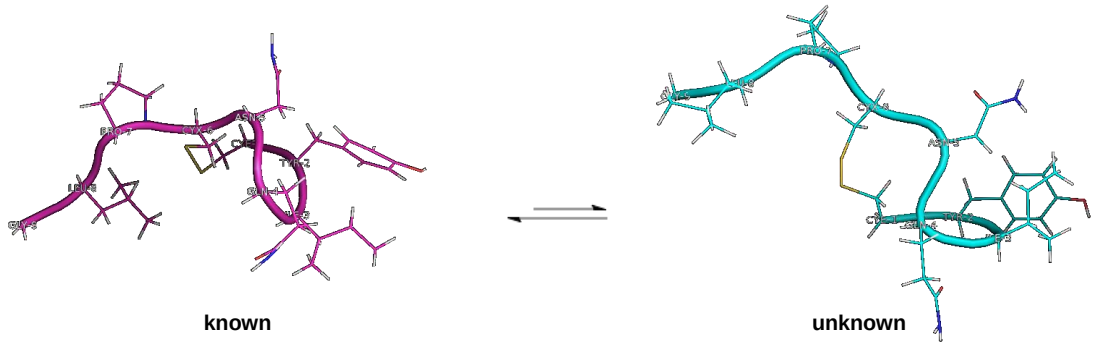

Extended molecular dynamics (MD) simulations (> 1 μs) show great promise in delivering significant, practically relevant, insight into conformational processes that occur within molecular systems. If long enough, MD simulations can reveal conformational interconversions particularly in peptides and proteins. Conformational equilibria may be unfavourable and dominated by the highly populated more stable conformation. However, the less favoured conformer is often the physiologically relevant one and may present significant difficulties for quantification by experimental techniques. Close coordination of MD analysis and experiment helps shed light on pharmacologically relevant molecular phenomena.

This work is part of a series of long-term MD simulations [1] (≥ 3 μs) applied to the cyclic nonapeptides oxytocin, 8-Arg-vasopressin, and deamino-oxytocin (dOT). Their moderate size and multitude of structural features presents an ideal test case to emphasize the necessity of extended simulations and to apply diverse conformational-analysis methods [2, 3].

The MD on dOT shows that (i) the results achieved with a runtime of 3 μs are in very good agreement with experimental data [4, 5] and (ii) employing DASH [2] in the analysis of these systems proves powerful and reliable in characterising conformational clusters. Furthermore, a previously undetected ring conformation of dOT was significantly populated in the simulation trajectory (390 ns/ 3000 ns, 8 transitions). This conformation indicates greater conformational flexibility of dOT vs. OT/ VP and thus helps explain its super-agonist properties [6].

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