SAT-722: Structure-Based Discovery of Hydraulic Fracturing Chemicals as Novel Androgen Receptor Antagonists

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Hydraulic fracturing (HF) technology is increasingly utilized for oil and gas extraction operations. The widespread use of HF has led to concerns of potential negative impacts on both the environment and human health. Indeed, the potential endocrine disrupting impacts of HF chemicals is one such knowledge gap. Herein, we used structure-based molecular docking to assess the binding affinities of 60 HF chemicals used in California to the human androgen receptor (AR). Five HF chemicals had relatively high AR binding affinity, suggesting the potential to disrupt AR effects. We next assessed androgenic and antiandrogenic activities of these chemicals in vitro. Of the five candidate AR ligands, only Genapol® X–100 was found to significantly reduce the AR transactivation by 22%. To better understand the structural effect of Genapol® X–100 on the potency of receptor inhibition, we compared the antiandrogenic activity of Genapol® X–100 with that of its structurally similar chemical, Genapol® X–080. Interestingly, both Genapol® X–100 and Genapol® X–080 elicited a significant antagonistic effect with 20% relative inhibitory concentrations (RIC20) of 0.43 and 0.89 µM, respectively. This indicated that Genapol® X–100 was more potent in inhibiting AR than Genapol® X–080, consistent with longer Genapol® X–100 chain length causing greater potency of AR activity inhibition. Furthermore, we investigated the mechanism of AR inhibition of these two chemicals in vitro. The result revealed that both Genapol® X–100 and Genapol® X–080 inhibited AR through noncompetitive binding mechanism. The effects of these two chemicals on the expression of AR responsive genes such as PSA, KLK2, and AR were also investigated. Genapol® X–100 and Genapol® X–080 notably altered the expression of these genes at relatively low concentrations of 0.5 µM to 1 µM. Using these integrated in vitro and in silico approaches, we identified HF chemicals as novel noncompetitive AR antagonists. Our findings heighten awareness of endocrine disruption by HF chemicals and provide evidence that noncompetitive antiandrogenic Genapol® X–100 could possibly cause adverse endocrine health effects in humans.