Structural insights into the high affinity binding of cardiotonic steroids to the Na⁺,K⁺-ATPase

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The Na⁺,K⁺-ATPase is the defined target for cardiotonic steroids. Binding of cardiotonic steroids to the enzyme causes inhibition of its functional activity and initiates intracellular signaling pathways. We describe here the crystal structures of the pig kidney Na⁺,K⁺-ATPase in its phosphorylated form in complex with two different cardiotonic steroids, ouabain and bufalin, at 4.6 and 4.1 Å resolution, respectively. The steroid binds to a site formed by transmembrane segments αM1 through αM6, plugging the ion pathway from the extracellular side. We show that the transmembrane segments αM1 and αM2 move towards the cardiotonic steroid molecule bound against the αM3 and αM4 segments and that this induced fit mechanism is crucial for high affinity binding of cardiotonic steroids to the Na⁺,K⁺-ATPase. We postulate that the overall conformation of the pump in the E2P state is the most favourable starting point for this induced fit. The consequences of the observed rearrangements of the Na⁺,K⁺-ATPase molecule for the protein-protein interactions within the signal transduction cellular networks are discussed.

References