Insights into Benzylisoquinoline Alkaloid Recognition Revealed by the 2.4 Å Crystal Structure of Codeionone Reductase

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The pharmaceutical properties of plant-derived compounds are widely used in modern day medicine. Benzylisoquinoline alkaloids (BIAs) are a class of secondary metabolites with a diverse range of chemical structures and physiological effects. Codeine and morphine are closely related BIAs with particularly useful analgesic properties. The aldo-keto reductase (AKR) codeinone reductase (COR) catalyzes the penultimate step in morphine biosynthesis in opium poppy (Papaver somniferum). After extensive optimization of crystal growth conditions, we have determined the structure of apo-COR (2.4 Å resolution) for the first time, using the structure of chalcone reductase as the search model for molecular replacement. The structure of apo-COR reveals a three-dimensional framework for understanding BIA substrate recognition and catalysis. Structural comparisons of COR to closely related plant AKRs and more distantly related homologues reveals a novel conformation in the β1α1 loop adjacent to the BIA binding pocket. The proximity of this loop to several highly conserved active site residues and the expected location of the nicotinamide ring of the NADPH cofactor suggest the importance of several key residues in BIA substrate recognition. The effects of mutations to residues in this loop and at other nearby positions help to define specific roles in substrate recognition and catalysis. Combined with the structure and COR, these findings from mutagenesis also help to suggest structure-function relationships in a second AKR critical to BIA biosynthesis, the 1,2 dehydroreticuline reductase domain in the critical enzyme reticuline epimerase.