Altitudinal differentiation in hemoglobin function in birds and small mammals

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Some of the best prospects for identifying mechanisms of hemoglobin (Hb) adaptation to hypoxia are afforded by mechanistic studies of Hb polymorphism in species that are continuously distributed across steep altitudinal gradients. Here we report the results of combined genetic and functional analyses of Hb polymorphism in two such species: (1) the rufous-collared sparrow (*Zonotrichia capensis*), a passerine bird that is distributed from sea level to elevations of >5000 m in the Andes of South America, and (2) the deer mouse (*Peromyscus maniculatus*), a murine rodent that is distributed from sea level to elevations of >4300 m in various mountain ranges of western North America. In both taxa, highland populations exhibit elevated Hb-O_2 affinities, and in both cases genetic variation in Hb function is attributable to multiple amino acid mutations that affect intrinsic O_2 affinity and the sensitivity of Hb-O_2 affinity to the inhibitory effects of allosteric effectors (organic phosphates and chloride ions). In the Hbs of higland sparrows and mice, suppressed sensitivities to allosteric effectors do not involve substitutions at known phosphate or chloride binding sites. We are currently using protein engineering experiments involving recombinant Hbs to gain insight into the structural mechanisms responsible for the observed functional changes.