Impact of climate change on water resources in mountainous headwater catchment of the Tarim River Basin (TRB), the largest inland river basin in China, was assessed by using VIC (Variable Infiltration Capacity) model. Performance of 25 GCMs (General Circulation Models) was evaluated. The statistical downsampling models were used to develop local climate change scenarios. Projected meteorological variables were inputted into the VIC model to simulate changes of hydrological regime. Impact of climate change on runoff in the catchment was assessed. Results showed that several GCMs had better abilities to reproduce most of statistical characteristics of the climate variables in the study area. GCMs simulate monthly temperature the best and precipitation the worst. NHMM and SDSM had abilities in downsampling daily precipitation, maximum and minimum air temperature in the TRB. It shows an obvious increasing trend for minimum and maximum air temperature in TRB, in which the magnitude of the increasing trend is the greatest for SRES A2, and the smallest for B1 scenario, with A1B scenario in-between. It shows a decreasing trend for precipitation in TRB in the future, with the magnitude of decreasing trend being smaller than 10% at all stations, and most of stations are smaller than 5%. Runoff in the headwater catchment (HC) tends to exhibit a decreasing trend under climate change in the future. Both precipitation and runoff for the HC show obviously increasing trend in April. This might be beneficial to the spring irrigation in the study area.