Freshwater organisms face multiple threats associated with anthropogenic transformations of their habitats (e.g., extraction, diversion), influx of nutrients and pollutants that accelerate eutrophication and hypoxia (low dissolved oxygen), in addition to overharvesting and species invasions. Further, there is mounting evidence that freshwater systems are highly sensitive to climate change; with rising water temperatures and intensification of hydrological cycles expected to impact freshwater species and communities across the globe. For fishes inhabiting freshwaters, relocation to more favourable habitats is not always possible (for example, if fish are in isolated lakes or drainages), and thus the adaptive capacity of fishes to respond in situ to multiple stressors may be critical to their persistence. Two stressors that are likely to have strong interactive effects on fishes (and fisheries) are thermal stress associated with climate warming and hypoxia because both affect the aerobic metabolism of fishes. Metabolic rate in fishes and other ectotherms tends to increase with increasing temperature. Hypoxia, however, limits the availability of environmental oxygen, rendering it more difficult to meet increased metabolic demands. Here, we examine the effects of two pervasive stressors (climate warming, hypoxia) on traits related to performance and fitness in fishes of the Lake Victoria Basin of East Africa. We focus on fishes of food security significance in addition to smaller “model” species that can be experimentally manipulated to quantify interactive effects of stressors. We also integrate the effects of fishing pressure with climate change and other stressors to determine potential synergistic consequences of multiple stressors on fish and fisheries. Our findings highlight the capacity for tropical freshwater fishes to respond to environmental change, and provide insight into the long-term sustainability of fish and fisheries in systems where fishes play a key role in livelihood stability and food security. We end by highlighting the importance of infrastructure for large and small-scale experimental studies, as well as training that is collaborative and integrative across levels of biological organization so that research is well positioned to inform fisheries policies and outcomes.