



Metabolic Adaptation to Hypoxia and Anoxia in Freshwater Teleosts: A Comparative Cellular Framework With Relevance to Indian River Systems

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Abstract:

Freshwater hypoxia spans transient reductions in oxygen partial pressure to complete anoxia, imposing a fundamental mismatch between mitochondrial ATP supply and cellular energy demand. This review integrates comparative teleost physiology, biochemical and molecular adaptations, and implications for Indian river systems using literature published by April 2023. It distinguishes compensatory oxygen acquisition, metabolic suppression, glycolytic substrate use, lactate management, ethanol-producing anaerobiosis, and tissue-specific neurocardiac preservation. Crucian carp and goldfish provide an exceptional, lineage-specific example in which duplicated metabolic machinery permits ethanol excretion, mitigating lactate accumulation during prolonged anoxia; this phenotype cannot be generalized to Indian carps. Indian air-breathing catfishes, snakeheads and climbing perch instead illustrate alternative solutions centred on aerial oxygen acquisition, flexible nitrogen handling and habitat-dependent regulation. We evaluate the hypoxia-inducible factor (HIF) system, cellular energy sensing, mitochondrial function, gill plasticity, substrate economics, oxidative stress during reoxygenation, and methodological limits of the critical oxygen tension (P_{crit}). A source-derived quantitative display documents reduced metabolic output in anoxic crucian carp brain slices, whereas all other schematics are conceptual. We propose an integrated assessment linking water-column oxygen dynamics to respirometry, tissue ATP balance, histology, enzyme activity, transcriptomics and recovery outcomes. The principal conclusion is that hypoxia resistance is a composite of acquisition, energy-demand regulation and survival, not a single universal molecular signature. Despite ecological relevance to the Ganga and other Indian systems, field-scale validation of these cellular pathways remains incomplete.

Key words: freshwater teleosts; hypoxia; anoxia; Carassius; metabolic suppression; ethanol fermentation; HIF; glycogen; Indian rivers; air breathing; P_{crit} ; reoxygenation

1. Introduction: oxygen limitation as a multi-scale problem

Dissolved oxygen availability varies with turbulence, temperature, primary production, microbial respiration, wastewater oxygen demand, flow intermittency and seasonal stratification. A fish inhabiting a warm, slow-moving tributary may encounter an oxygen trajectory fundamentally different from that experienced in a cold, turbulent headwater. These environmental contrasts require separating dissolved oxygen concentration (mg L^{-1}), saturation and oxygen partial pressure (PO_2), because the physiological diffusion gradient is determined by partial pressure rather than concentration alone (Fry, 1971; Richards, 2009; Zhang and Farrell, 2022).

Hypoxia denotes oxygen availability below that needed to support particular physiological processes; its ecological threshold is therefore species- and endpoint-dependent. Anoxia, in contrast, denotes effectively absent molecular oxygen. These should not be conflated: much of the fish literature quantifies hypoxic exposure and aerobic performance rather than survival under verified complete anoxia (Richards, 2010; Reemeyer and Rees, 2019).

Animal responses are hierarchically organised. Ventilation and circulation may initially maintain uptake; altered behaviour and oxygen-binding properties may extend aerobic function; and if delivery remains insufficient, glycolytic ATP generation, substrate mobilisation and suppression of expensive cell functions determine survival time. Mechanisms established in one taxon cannot be transferred automatically to Indian river fauna because phylogenetic history, respiratory anatomy, season, body size and temperature profoundly affect resilience (Nilsson and Renshaw, 2004; Mandic et al., 2009; Zhu et al., 2013).

2. Review scope, source selection and interpretive limits

This is a structured critical narrative review of source-identifiable research dated no later than April 2023, not a prospectively registered systematic review or new meta-analysis. The evidence emphasis is on direct biochemical and physiological experiments in freshwater teleosts, mechanistic oxygen-sensing research, and documented air-breathing adaptations relevant to South Asia. Comparative studies of marine fish and general vertebrate HIF biology are included only to explain mechanisms and explicitly separated from Indian freshwater empirical findings. No PRISMA counts or pooled effect sizes are claimed.

Inference is categorised as direct freshwater-fish experimental evidence, comparative fish evidence, broader vertebrate

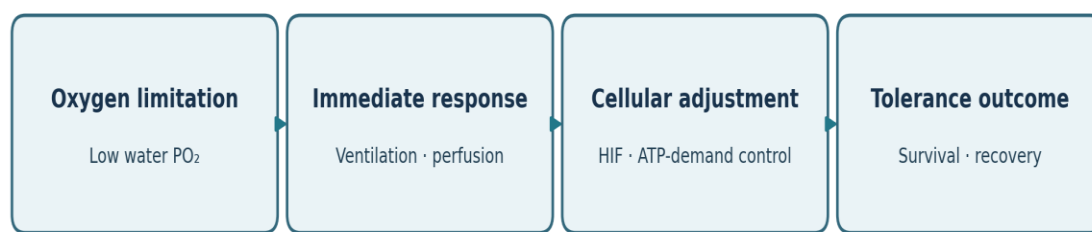
molecular biology, or proposed application to Indian rivers. Quantitative claims are included only where source-specific data are identifiable. The review deliberately avoids generating synthetic Pcrit ranges or assigning measured anoxia survival to poorly sampled Indian species (Richards, 2009; Xiao, 2015; Abdel-Tawwab et al., 2019).

3. Oxygen supply, respiratory phenotypes and whole-animal performance

The oxygen cascade connects water-to-gill transfer, perfusion, blood oxygen loading, tissue oxygen delivery and mitochondrial oxygen utilisation. Under declining ambient PO₂, a fish can change ventilatory volume, lamellar perfusion, surface exposure and cardiac output, often at substantial energetic cost. Although oxygen extraction can be enhanced, the capacities of each component are finite, and elevated temperature simultaneously raises resting oxygen demand and reduces oxygen solubility (Pörtner and Farrell, 2008; Mandic et al., 2009; Nilsson et al., 2012).

Pcrit is the ambient oxygen tension at which a specified benchmark oxygen-uptake rate can no longer be maintained. It is valuable for comparing aerobic oxyregulation when standard metabolic rate, measurement protocol and curve fitting are standardised; it should not be interpreted as the oxygen tension for loss of equilibrium, reproductive failure or absolute survival. Reemeyer and Rees (2019), Zhang et al. (2021) and Zhang and Farrell (2022) show why multiple performance endpoints provide a more complete hypoxia phenotype. Pcrit can also shift with temperature, body size, elevated CO₂ and respirometer conditions.

In a cross-species synthesis, different measures of hypoxia tolerance are only partially interchangeable. Rates of oxygen uptake, time to loss of equilibrium, blood oxygen affinity, behavioural aquatic-surface respiration and capacity for anaerobic ATP supply probe different processes. The literature on hypoxia-sensitive and tolerant fishes highlights oxygen extraction and access to alternate gas-exchange environments as ecologically consequential adaptations (Mandic et al., 2009; Richards, 2011; Graham, 1997).



Conceptual sequence; response timing and extent vary across teleost lineages.

Figure 1. Original conceptual synthesis of the hierarchy from aquatic oxygen limitation through compensatory acquisition and cellular regulation to survival. This is a proposed mechanistic schematic, not a plot of measured Indian river data.

4. Bioenergetic arithmetic: ATP supply–demand matching

Aerobic oxidative phosphorylation provides far more ATP per glucose than glycolytic substrate-level phosphorylation. Under severe hypoxia, limitation of terminal electron acceptance constrains mitochondrial ATP flux, and survival depends on both the remaining ATP-generating capacity and a coordinated reduction in ATP demand. Glycolysis alone cannot indefinitely preserve tissue ATP at normoxic demand levels because carbohydrate stores are finite and end-product accumulation can disturb intracellular pH and other cellular processes (Richards, 2009, 2010; Hochachka and Somero, 2002).

ATP-demand reduction can involve lower ion-pumping requirements, suppression of protein synthesis, altered channel conductance, reduced contractile or locomotor work, and selective preservation of essential electrophysiological activity. Such adjustments differ among tissues. Neural tissue must preserve electrochemical gradients, and cardiac tissue must sustain at least sufficient perfusion for nutrient delivery and metabolite removal; hence genuine whole-body metabolic depression is not synonymous with universal shutdown of ATP use (Nilsson, 2001; Lutz and Nilsson, 2004; Stecyk et al., 2004).

Direct calorimetry measures heat production and can capture overall metabolic suppression when oxygen uptake is no longer an adequate proxy. In isolated crucian carp telencephalic slices, Johansson et al. (1995) reported a 37% reduction in heat output, corresponding to an estimated 31% reduction in ATP turnover during anoxia, with adenylate energy charge maintained. This is a tissue-specific, preparation-specific result, not a whole-fish estimate or an Indian freshwater measurement.

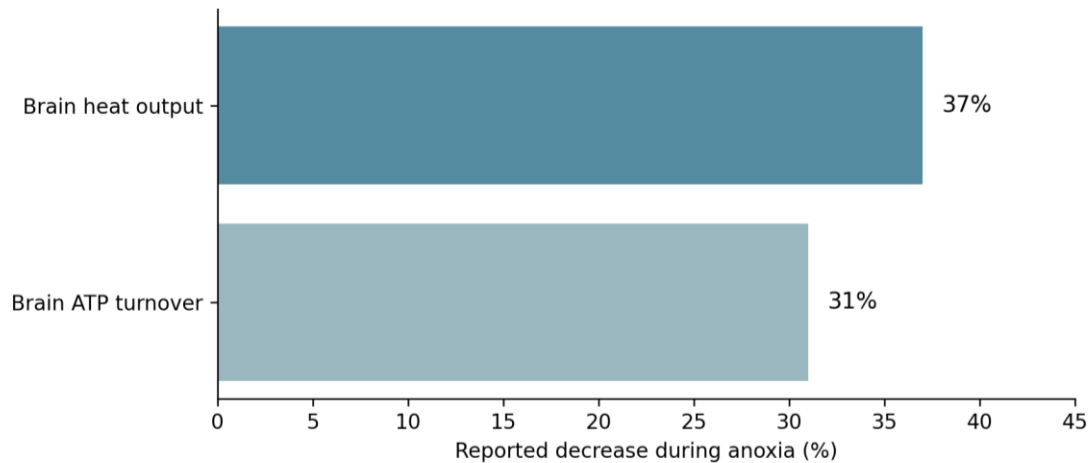


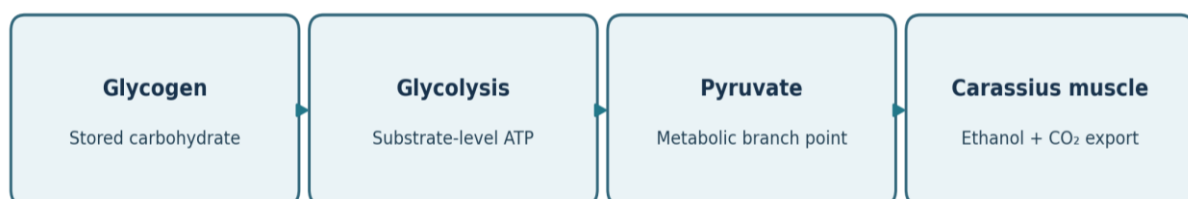
Figure 2. Redrawn literature-derived chart showing the reported reductions in heat output (37%) and estimated ATP turnover (31%) in isolated crucian carp brain slices during anoxia, after Johansson et al. (1995). These are source-specific tissue measurements, not pooled estimates or observations in Indian river fishes.

5. *Carassius* ethanol production: an exceptionally derived solution

A hallmark of crucian carp and goldfish is the ability to channel carbohydrate-derived carbon toward ethanol, which is released across the gills instead of being retained as large amounts of lactate. The classic study by Shoubridge and Hochachka (1980) identified ethanol as a vertebrate anaerobic end product. The detailed physiological synthesis by Vornanen et al. (2009) establishes that this strategy depends on unusually substantial glycogen reserves and is strongly influenced by temperature and seasonal acclimation.

The significance of ethanol production is not that anaerobic glycolysis becomes energetically equivalent to aerobic respiration. Rather, exporting a diffusible end product can moderate accumulation of acid-associated metabolites and facilitate a prolonged, carbohydrate-dependent anaerobic strategy. The carbon route depends on specialised muscle metabolism; other tissues retain distinct anaerobic intermediates and send carbon substrates through systemic circulation. These distinctions are crucial when interpreting tissue lactate assays or extrapolating from liver to skeletal muscle (Nilsson and Renshaw, 2004; Vornanen et al., 2009).

In contrast, a typical Indian cyprinid fish should not be described as ethanol-producing simply because it belongs to Cypriniformes. The defining molecular changes supporting this pathway have been demonstrated for particular *Carassius* lineages, so claims about Indian Labeo, Catla or Cirrhinus require direct enzyme, isotope-tracer and metabolite evidence rather than family-level inference. Complete anoxia survival is likewise not interchangeable with routine tolerance of oxygen-poor pond or river water.



Simplified biochemical pathway; specialized ethanol synthesis is not a universal freshwater-fish trait.

Figure 3. Original conceptual mechanistic synthesis of simplified anaerobic carbon routing in *Carassius*, informed by Shoubridge and Hochachka (1980) and Vornanen et al. (2009). The diagram does not depict a directly measured pathway in Indian freshwater species.

6. Oxygen sensing, HIF regulation and gene expression

The canonical HIF system links intracellular oxygen to adaptive transcription. At adequate oxygen availability, prolyl hydroxylase activity facilitates HIF- α hydroxylation, von Hippel–Lindau recognition and proteasomal turnover. Lower oxygen can limit hydroxylation and permit HIF- α accumulation, nuclear dimerisation with HIF- β , recruitment of transcriptional cofactors and regulation of genes involved in glycolysis, vascular responses and oxygen homeostasis. These molecular principles are well established in broader vertebrate biology, although species-specific isoform regulation varies among teleosts (Schofield and Ratcliffe, 2004; Semenza, 2012; Xiao, 2015).

Fish genomes can retain multiple HIF isoforms arising from evolutionary duplication; their functions are not necessarily interchangeable. Rytönen et al. (2013) described cyprinid HIF subfunctionalisation, while Chi et al. (2013) documented evolutionary diversification across early ray-finned and lobe-finned branches. Expression profiles therefore require careful

selection of tissue, exposure stage and paralog identity. Upregulation of hif mRNA should not be treated as a measurement of protein stability or target-gene transcriptional activity.

Regulatory crosstalk complicates mechanistic attribution. Protein synthesis, redox signalling, inflammation and energy-state regulation can affect hypoxia-responsive transcription, as established in general molecular studies (Majmundar et al., 2010; Greer et al., 2012; Aragonés et al., 2009; Rius et al., 2008). Detecting HIF expression in an Indian fish sample may indicate oxygen-related stress, but does not independently distinguish hypoxia from infection, xenobiotic exposure or sampling artefacts.

7. Mitochondrial function and reoxygenation injury

Mitochondrial oxygen limitation constrains respiratory-chain flux, redox balance, substrate oxidation and ATP production. Adaptation may entail changing mitochondrial density, substrate preference, respiratory capacity or the coupling of ATP demand to supply. The relevant experiment must distinguish reduced oxygen availability from reversible metabolic reprogramming and irreversible tissue injury (Richards, 2009; Hochachka and Somero, 2002; Xiao, 2015).

Reoxygenation is not invariably benign. Restoration of oxygen can increase reactive oxygen production after substrate accumulation and disturbed electron transfer; antioxidant defences and recovery processes may thus determine survival beyond the hypoxic interval. Changes in catalase, glutathione or lipid-peroxidation biomarkers are nonspecific, so mechanistic work should integrate mitochondrial respiration, oxidative damage, ATP recovery and tissue function rather than claim causal oxidative injury from a single marker (Bickler and Buck, 2007; Abdel-Tawwab et al., 2019).

8. Gill remodelling, ion regulation and tissue trade-offs

Branchial restructuring can alter oxygen exchange area and diffusion distances. Depending on species and context, expanding exposed lamellar area can improve oxygen uptake but increase ion and water flux, pollutant contact, or energetic maintenance costs. Conversely, reduced exposed surface during benign conditions may limit osmotic loading, but restrict oxygen uptake during rapid oxygen decline. Nilsson et al. (2012) reviewed the plasticity of gill structure, while Turko et al. (2012) demonstrate the respiratory trade-offs associated with remodelling during terrestrial acclimation in amphibious fish.

Morphological remodelling is not a universal hallmark of hypoxia tolerance. Surface respiratory behaviour, aerial breathing, globin affinity and regulation of perfusion may predominate in other lineages. Gross gill morphology alone is insufficient to infer active oxygen consumption; functional validation with blood gases, respirometry and ion flux remains necessary (Graham, 1997; Richards, 2011).

9. Comparative teleost strategies: separating shared mechanisms from exceptions

Table 1. Comparative strategies and evidence limits (Shoubridge and Hochachka, 1980; Mandic et al., 2009; Graham, 1997; Turko et al., 2012).

Model / ecological context	Primary reported strategy	Evidence status	Caution
Crucian carp (<i>Carassius carassius</i>)	Glycogen storage, metabolic depression, ethanol export	Direct anoxia experiments and synthesis	Exceptional lineage; temperature-dependent
Goldfish (<i>Carassius auratus</i>)	Ethanol-producing anaerobiosis; hypoxia-responsive globins	Direct comparative physiology	Not a proxy for all cyprinids
Hypoxia-tolerant sculpins	Oxygen extraction and Pcrit-associated ecological segregation	Comparative multi-species analysis	Includes marine/intertidal taxa
Indian air-breathing teleosts	Accessory air exchange; species-specific nitrogen excretion	South Asian comparative physiology	Air breathing ≠ proven long-term anoxia survival
Amphibious <i>Kryptolebias</i>	Plasticity of gill structure with aquatic respiratory cost	Direct experimental observations	Not Indian freshwater field evidence

10. Relevance to Indian river and floodplain systems

Seasonal monsoon discharge, floodplain isolation, nutrient enrichment, wastewater oxygen demand and thermal extremes create multiple pathways to low oxygen in Indian freshwater environments. Yet continuous oxygen records and paired cellular assays remain patchy for many inland taxa. It is therefore more defensible to identify mechanistic hypotheses for Indian systems than to claim that globally investigated mechanisms are already confirmed in particular stretches of the Ganga, Yamuna, Brahmaputra or peninsular rivers (Diaz, 2001; Breitburg et al., 2018).

In tropical urban and peri-urban river reaches, agricultural runoff and untreated or inadequately treated municipal

wastewater introduce biodegradable organic matter and nutrients, increasing biochemical oxygen demand (BOD) and microbial oxygen consumption. Under low-flow, warm conditions this loading can intensify diel dissolved-oxygen variation, including short-lived nocturnal or predawn hypoxia; such episodic hypoxia should not be equated with sustained, verified complete anoxia. The Mula–Mutha river system around Pune provides a relevant peninsular example of urban sewage and spatially variable water quality: Vyas et al. (2022) assessed seasonal and spatial physicochemical conditions, including DO and BOD, across eight monitoring sites. The available observations support a local pollution-exposure context, but do not establish a numerical frequency of hypoxic spikes or demonstrate complete seasonal anoxia.

The Indian subcontinent includes air-breathing forms such as *Anabas testudineus*, *Heteropneustes fossilis*, *Clarias batrachus* and several *Channa* species. Accessory breathing structures permit some species to supplement aquatic gas exchange when water oxygen is limiting, but air access requirements, dependence and performance vary across taxa and life stages. Aerial oxygen uptake must be measured, or experimentally restricted under ethically approved protocols, before attributing survival to cellular anoxia tolerance (Graham, 1997; Ip et al., 2001; Chew and Ip, 2014).

Nitrogen metabolism is a distinct adaptive dimension. Altered ammonia handling, ureogenesis and air exposure may interact with hypoxic habitats, yet detoxification of ammonia is not mechanistically identical to maintenance of ATP production during anoxia. Indian studies should therefore separate branchial oxygen acquisition, aerial breathing, acid–base regulation, nitrogen excretion and intracellular energetic adaptation in the same biological model when feasible (Ip et al., 2001; Chew and Ip, 2014).

10.1. Species selection and generalisability

Rohu, catla and mrigal are economically important fish, but their physiological responses cannot be inferred from European *Carassius* solely because they share a broad cypriniform ancestry. Likewise, *Heteropneustes* and *Channa* differ anatomically and may not share identical hypoxia-response profiles. Future field studies should select sympatric water-breathing and air-breathing species across the same oxygen gradient and control body size, sex, reproductive state and thermal history.

10.2. Co-stressors and exposure attribution

In eutrophic low-flow waters, oxygen reduction often co-occurs with ammonia, CO₂ accumulation, suspended solids and chemical contamination. Such covariates affect ventilation, ionoregulation, endocrine responses and mortality. A controlled laboratory experiment that manipulates only dissolved oxygen can illuminate direct physiological mechanisms, while real river causation requires multivariable field data (Wu, 2002; Abdel-Tawwab et al., 2019; Reemeyer and Rees, 2019).

For sewage-affected urban reaches such as the Mula–Mutha, single daytime grab samples may overlook oxygen minima occurring before dawn. Continuous high-frequency DO and temperature logging alongside BOD, nutrient and discharge measurements would permit separation of brief hypoxic excursions from prolonged oxygen deprivation before inferring cellular anoxia adaptations.

11. Integrated methods to test cellular adaptation

An appropriate study begins with quality-assured dissolved oxygen and temperature time series, ideally including predawn minima, seasonal transitions and flood recession. Laboratory tests should then quantify standardized oxygen uptake, P_{crit} where suitable, time to loss of equilibrium under predetermined humane endpoints, recovery rate, and air-breathing behaviour in relevant species. Water PO₂, chamber CO₂, pH, fish mass, activity, feeding state and acclimation require explicit control (Reemeyer and Rees, 2019; Zhang and Farrell, 2022).

Cellular comparisons can measure tissue ATP, ADP and AMP, glycogen, lactate, glucose and pH alongside LDH activity, mitochondrial respiration, HIF protein accumulation and target transcripts. Where ethanol production is hypothesised, gas chromatography or validated enzymatic assays should detect ethanol in tissue, plasma and water, with labelled-substrate experiments distinguishing endogenous production from microbial contamination. Tissue sampling must be immediate and standardized to avoid post-capture metabolic artefacts (Johansson et al., 1995; Shoubridge and Hochachka, 1980).

Genome-wide and transcriptomic datasets may identify paralog- and tissue-specific responses, but apparent expression differences must be separated from acclimation, lineage effects, batch, oxygen exposure, and cell-composition changes. Metabolomic signatures without measured respiratory performance provide mechanistic leads rather than complete evidence of tolerance. Replication should occur at the independent tank level when fish share the same experimental treatment vessel (Xiao, 2015; Rytönen et al., 2013).



Proposed study design, not results of a new field experiment.

Figure 4. Original conceptual synthesis proposing an integrated environmental, whole-organism and cellular evidence pathway for Indian freshwater research. This is a recommended study design, not an empirical dataset or a redrawn literature-derived result.

Table 2. Recommended endpoint matrix; proposed synthesis, not results from new Indian river sampling.

Variable	Recommended measurement	Major confounding factor	Interpretive value
Ambient exposure	Continuous DO, PO ₂ , temperature, pH, CO ₂	Diel and flow variability	Defines oxygen stress history
Whole-fish uptake	Intermittent-flow respirometry, Pcrit	Handling, mass, chamber respiration	Aerobic regulatory threshold
Behaviour	Air-gulping, aquatic surface respiration, equilibrium	Predator cues, activity, access to surface	Acquisition and loss-of-function response
Brain energetics	ATP/ADP/AMP, glycogen, lactate, microcalorimetry	Sampling delay and tissue isolation	Tests ATP balance and demand
HIF regulation	Protein stabilization plus target transcripts	Cell mix, redox and pollutants	Tests oxygen signalling
Anaerobic route	Ethanol and lactate with isotope tracer	Microbial ethanol, water diffusion	Tests Carassius-like mechanism
Recovery	ATP restoration, behaviour, tissue injury	Reoxygenation rate and temperature	Separates survival from sustained damage

12. Quantitative interpretation and evidence grading

The only newly drawn empirical bar chart in this review is a transparent reproduction of the two percentages reported for isolated crucian carp brain slices by Johansson et al. (1995). It must not be generalised to whole fish, to all tissues, or to Indian river taxa. Across broader literature, raw Pcrit values cannot be averaged without matching oxygen units, measurement protocols, standard metabolic rates and fish traits. Any future meta-analysis would require primary data extraction and between-study heterogeneity modelling (Richards, 2010; Reemeyer and Rees, 2019).

Table 3. Evidence-to-claim safeguards.

Evidence category	Representative publications	Supported inference	Unsupported leap
Direct anoxia biochemistry	Shoubridge & Hochachka 1980; Johansson et al. 1995	Carassius-specific anaerobic metabolism	All cyprinids ferment to ethanol
Comparative fish tolerance	Mandic et al. 2009; Richards 2011	Physiological diversity and oxygen extraction	Single universal tolerance index
Cellular HIF biology	Semenza 2012; Xiao 2015	Oxygen-responsive transcriptional pathways	Transcript increase proves survival
Indian/South Asian relevance	Graham 1997; Ip et al. 2001; Chew & Ip 2014	Air-breathing and nitrogen-metabolism context	Complete anoxia survival in every species
Proposed river study	Present synthesis	Testable integrated design	Existing multi-river outcome data

12.1. Comparative boundary cases and external validity

Aquatic hypoxia research in oceanic and coastal fishes establishes broader ecological boundary conditions without supplying species-specific Indian freshwater endpoints. Diaz (2001), Diaz and Rosenberg (2008) and Breitburg et al. (2018) document the significance of expanding aquatic oxygen deficits, while Domenici, Herbert and Lefrançois (2007), Claireaux and Lagardère (1999) and Almeida-Val et al. (2006) provide complementary frameworks for locomotor impairment, environmental performance and Amazonian fish adaptations. Their results are comparative context, not direct observations in Indian rivers.

Neural preservation, blood oxygen transport and oxygen-signalling gene duplication further emphasise the uneven distribution of adaptive traits. Lutz and Nilsson (2004) synthesize tissue-specific brain protection; Roesner et al. (2008) describe goldfish globins; and Chi et al. (2013) together with Rytönen et al. (2013) discuss HIF evolutionary diversification. Such evidence warrants separate consideration of oxygen storage and binding, membrane excitability and transcriptional regulation rather than folding these distinct functions into a single antioxidant or HIF score. Historical foundations of environmentally contingent metabolic regulation are provided by Fry (1971), whereas Hochachka and Somero (2002) offer its broader biochemical evolutionary context.

13. Future research priorities

First, oxygen exposure must be recorded at the spatial and temporal resolution experienced by fishes. Second, Indian freshwater fish studies should measure oxygen acquisition and cellular ATP economics concurrently, including genotype- and acclimation-aware designs. Third, anoxia should be experimentally verified and distinguished from mild hypoxia. Fourth, multi-day recovery and delayed neurological or reproductive effects should complement survival endpoints. Fifth, regional datasets should explicitly investigate whether species-specific air breathing, ion transport and nitrogen metabolism offer alternative solutions to oxygen limitation rather than search for a universal *Carassius*-like fermentative pathway (Nilsson and Renshaw, 2004; Zhu et al., 2013; Abdel-Tawwab et al., 2019).

14. Conclusions

Teleost responses to low environmental oxygen reflect integration of respiratory acquisition, tissue-specific energy economics, molecular sensing and metabolic end-product management. The extraordinary anoxia tolerance of crucian carp is informative precisely because its ethanol-producing phenotype is exceptional. Most Indian river fishes should instead be studied as distinct physiological systems, especially where air-breathing capacity, variable water quality and altered nitrogen handling interact. The strongest future evidence will link continuously measured river oxygen exposure to experimentally validated respiratory performance, tissue energy states, molecular responses and recovery. Such research can bridge a major gap between established comparative fish physiology and Indian river-system conservation without overstating presently available India-specific cellular evidence.

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