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Divergent and Convergent Protein-Sparing Strategies During Fasting Adaptation Among Selected Bilaterian Taxa and the Effects of Oxidative Stress

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Abstract

This paper takes the protein-sparing effect as its center and argues that this metabolic strategy, already well studied in human fasting adaptation, is, in fact, a general logic of energy allocation widely shared within Bilateria (bilaterian animals). The effect can be taken apart into two levels. One level is a set of highly conserved upstream mechanisms. The mammalian-derived three-phase starvation model "glycogen-gluconeogenesis-protein-sparing" serves as a comparative heuristic for cross-species analysis, and this tri-phasic pattern has been empirically documented in a limited number of taxa. Additional conserved components include the glucose-sparing fuel pathway mediated by ketone bodies and the AMPK/mTOR nutrient-sensing axis, which is nearly universally conserved across eukaryotes. The other level is the downstream execution, which clearly diverges. The paper discusses how far sparing goes depending on the size of non-protein energy reserves, provides evidence of tissue specificity and timing, and examines several extreme phenotypes. Recent studies on a few particular lineages are brought together, and a picture emerges in which different molecular routes converge on the same end. The paper also analyses the roles of reactive oxygen species (ROS) and oxidative stress within this system from a relatively novel perspective. This proposed coupling remains to be validated by systematic experimental testing. The paper ends with what the strategy may suggest, in a biomimetic sense, for alternative protein production systems such as cultured meat and microbial protein fermentation.

Keywords

protein-sparing, fasting adaptation, convergent evolution, AMPK/mTOR pathway, ROS, and oxidative stress

1. Introduction

When energy intake is interrupted for a long period, an organism faces a central trade-off for survival: how to maintain basic physiological functions while delaying the breakdown of structural proteins, such as those in skeletal muscle. The protein-sparing effect is exactly this kind of adaptive metabolic strategy. Fat reserves are mobilized first, and ketogenesis takes over as the fuel source, so the demand for glucose falls; gluconeogenesis then draws fewer amino acids from muscle, and protein breakdown is indirectly held back [1]. The strategy has been well studied in human fasting adaptation [1]. This paper argues that it is not a specialized human adaptation but rather a general energy allocation strategy, potentially shared widely across Bilateria. However, existing comparative datasets suffer from notable sampling and publication biases: most available evidence

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comes from fasting-tolerant vertebrate species, while invertebrate data remain sparse [2]. Species exhibiting pronounced protein-sparing phenotypes are also more likely to be reported in the literature, potentially overrepresenting the prevalence of this trait across bilaterian taxa [3]. These limitations should be borne in mind when drawing broad evolutionary-scale inferences.

Metabolic depression caused by food deprivation has been recorded across the whole of Bilateria. However, the biochemical details of protein sparing are still best described in animals with differentiated muscle [2]. Pickard points out that the scarcity of essential amino acids (EAA) is an important selection pressure driving animals towards particular patterns of protein use [3]. This paper suggests that the strength of the "sparing" effect the pressure can produce probably depends on whether a lineage holds a structural protein pool. In groups with highly differentiated muscle, the muscle itself serves as an amino acid store that can be sacrificed and then rebuilt once feeding resumes. In groups lacking such a structure, the comparison behind the word "sparing" may not even hold.

A wide range of studies has confirmed the influence of fasting on ROS levels inside organisms. Recent work suggests that antioxidant pathways may contribute to protein protection during fasting, but the extent of this contribution varies by tissue and species, and no common rule has emerged. This raises three unresolved comparative-physiology questions: (1) Are altered ROS dynamics a causal driver, a secondary consequence, or merely a correlative by-product of fasting-associated protein remodeling? (2) Are observed ROS-protein-sparing relationships derived from cellular-level assays translatable to whole-organism adaptive phenotypes? (3) Can ROS measurements obtained using distinct probes across disparate tissues be directly compared among divergent taxa? The inter-relationship between ROS signaling and protein-sparing, as well as its lineage-specific manifestations, therefore, remains an important target for future systematic comparative investigation.

2. Homologous Conservation and Parallel Co-Option of Protein-Sparing Mechanisms (Evolutionary Scenarios for Shared Physiological Traits)

2.1 Cross-species Conservation of the Three-phase Starvation Model (Phenotypic Framework)

Metabolic change during long human fasting divides clearly into three continuous phases: an early phase in which blood glucose is held up by hepatic glycogen breakdown (about 0–24 h), a gluconeogenic phase in which muscle protein is broken down mainly to supply amino acid precursors, these amino acids entering gluconeogenesis together with lactate, pyruvate and the glycerol released by hydrolysis of triglycerides, and a final "protein-sparing" phase, dominated by fat mobilisation and ketogenesis, where protein breakdown is strongly suppressed. Urinary urea excretion is high early in the fast and then declines steadily, reflecting a metabolic shift from "spending protein to get glucose" to "saving protein and living on fat" [1]. The three-phase model was described systematically in clinical human fasting studies. Its core logic, which is to use the fast-acting store first, turn to the structural store next, and in the end survive in the way that wastes the least nitrogen, has been observed again and again during long starvation in insects, fish, amphibians, birds, and mammals, and this shows that the conservation of such an energy-allocation logic reaches across a fairly long evolutionary distance.

2.2 The Metabolic Mechanism of Ketogenesis (Biochemical Cascade)

The key mechanism sustaining the protein-sparing phase is indirect tissue protection conferred by ketone metabolism acting as a "glucose-sparing fuel". This physiological cascade comprises three distinguishable biochemical events: (i) elevated ketone-body synthesis triggered by enhanced fat mobilization; (ii) increased ketone utilization by the brain and other peripheral tissues, which reduces systemic glucose demand; (iii) consequent reduction of amino-acid supply requirements for gluconeogenesis, leading to indirect preservation of muscle protein [1]. Fat mobilization, ketogenesis, and protein breakdown represent largely independent pathways, coordinated via the shared glucose-insulin-ketone signaling axis. Declining insulin relieves inhibition of lipolysis; surplus acetyl-CoA derived from lipid mobilization fuels ketogenesis; rising circulating ketone concentrations, in turn, decrease the glucose dependence of the brain and peripheral tissues, alleviating the demand for amino-acid substrates for gluconeogenesis. Importantly, these three components do not always

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co-occur across taxa: elevated circulating ketone bodies can arise during fasting in many lineages equipped with adipose tissue and a ketogenic liver, yet robust cerebral ketone uptake and suppressed whole-body protein catabolism are not universally observed [2]. Where all three components are realized, this ketone-driven cascade provides a concrete biochemical explanation for the three-phase phenotypic pattern described in 2.1.

2.3 The AMPK and mTOR Axis: A Conserved Molecular Basis for Regulating Nutrient State and Protein Homeostasis (Molecular Signaling Framework)

At the cellular level, AMPK and mTOR represent two mutually antagonistic signaling hubs that sense nutrient availability and modulate the balance between protein synthesis and degradation. AMPK acts as an energy-deprivation sensor, whereas mTOR integrates nutrient and growth signals to drive protein-synthetic programs. In simplified cell-culture models, nutrient shortage triggers AMPK activation, which suppresses mTOR activity; this, in turn, represses protein synthesis while up-regulating autophagy and protein-degradation-associated gene expression. However, this canonical linear cascade represents an in vitro simplification and cannot be uncritically extrapolated to whole-animal fasting physiology. In living organisms, the functional outputs of AMPK, mTORC1, and autophagy do not follow a fixed, uniform sequence. Their combinatorial effects vary across tissues and shift dynamically at different stages of fasting. Critically, autophagy induction does not necessarily result in whole-body protein wasting: autophagy can mediate local organelle turnover and intracellular metabolite recycling within cells, without generating net systemic protein loss. Under nutrient-replete conditions, the signaling balance shifts in the opposite direction. From an evolutionary perspective, homologous components of both pathways are found in nearly all eukaryotes, albeit with variable degrees of sequence and functional conservation. Core ancestral components of the AMPK pathway have prokaryotic homologs, indicating its origin predates eukaryotes. In contrast, the TOR complex is considered a eukaryotic innovation that emerged alongside the eukaryotic cellular transition [4]. The phenotypic and metabolic conservation described in Sections 2.1 and 2.2 thus finds molecular correlates within these ancient signaling modules. Even so, functional conservation during fasting cannot be assumed a priori and must be evaluated on a case-by-case basis for individual animal lineages.

3. Divergence in Execution: Reserve Capacity, Tissue Specificity, and Extreme Phenotypes

The cases reviewed in this section span several lineages and are described in detail in the literature. To make the cross-case comparison transparent and to avoid repetitive narration, Table 1 lists, for each taxon, the reserve state, the fasting regime, the protein-sparing indicator, the ROS indicator (where available), and the principal limitation of the evidence. The text below explains only the cross-case patterns and the constraints on generalizing from them.

Table 1: Comparative summary of the fasting studies reviewed in Section 3

Taxon / study	Reserve state	Fasting regime	Protein-sparing indicator	ROS indicator	Evidence limitation
Insects (grasshopper, cockroach, moth larvae, darkling beetle) [5]	Lipid stores	Lethal starvation (days)	13C-breath protein oxidation	—	Five species only; no mechanistic explanation
Long-fasting birds & mammals [6]	Fat reserves	Long-term fasting	Protein-derived energy share; urinary nitrogen	—	Cross-species comparison, not same individuals; end-stage mechanism unresolved
Obese vs lean rats [7]	Fat and protein	Prolonged fasting	Protein loss; urinary nitrogen	—	Groups compared after fasts of different length
Humans, semi-starvation [8]	Fat and protein (rp)	Semi-starvation	Partitioning between fat and protein	—	Observational; human constraints

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Taxon / study	Reserve state	Fasting regime	Protein-sparing indicator	ROS indicator	Evidence limitation
Cuttlefish S. officinalis [9]	Limited carbohydrate and fat	Food withdrawal	Protein synthesis; degradation indices	—	Degradation indices indirect
Teleost S. lalandi [10]	Lipid	35-day sub-lethal starvation	Isotopic amino-acid signal, muscle vs liver	—	No direct synthesis/degradation rates
Carp C. carpio [11]	Lipid	3 vs 7 days	Muscle protein degradation	ROS (temporal)	Single species, single short fast
Ground squirrel I. tridecemlineatus [12]	Fat	Hibernation torpor	Not measured	H2S/SQR; mitochondrial respiration	Indirect; no protein-turnover data
Aestivating frog C. alboguttata [13]	Fat	6–9 months aestivation	Muscle atrophy; contractile force	Antioxidant defence (control level)	Protein structure inferred, turnover not measured
Nematode C. elegans [16]	Fat	Fasting–refeeding	Not measured	Redox state (H_2O_2 sensor, multiple tissues)	No protein-sparing indicator

3.1 Non-protein Reserve Capacity Sets the Ceiling of Sparing: Evidence Between and Within Species

How far protein sparing goes is not a fixed property set directly by taxonomy. It rises with the non-protein energy reserve capacity a lineage has accumulated during evolution. The larger the reserve, the more complete and the more sustainable the sparing; as reserve capacity approaches zero, the sparing mechanism itself degenerates with it.

Among insects, McCue et al. tracked five species by 13C breath testing [5]. The common pattern was that most species lowered the proportion of protein oxidation during starvation, but the magnitude and the persistence of the reduction differed markedly: the reduction reached significance only in the grasshopper (*Romalea microptera*), the cockroach (*Gromphadorhina portentosa*), and the larvae of the hawk moth (*Manduca sexta*), the last reaching its lowest value only at the end of starvation, whereas the darkling beetle larvae (*Zophobas morio*) never brought protein oxidation below its pre-starvation level. The authors provided no mechanistic explanation for this species difference, and because only five species were examined, the study is not intended to be exhaustive of insect strategies; it suffices to show that the ability to adjust protein oxidation under stress does differ among insects.

Cherel and Groscolas analyzed long-fasting birds and mammals. They showed that individuals with low fat reserves could not enter an effective protein-sparing phase from the beginning, and individuals with intermediate reserves could start sparing but only for a limited time; compared across species, the fattest species could push the share of energy coming from protein down to about 4%, against about 40% in the leanest ones [6]. The end of the sparing phase, that is, the stage where protein use rises again, is not the result of fat being fully exhausted: the paper notes that about 18–25% of the initial fat store remains when this stage begins. The authors suggest that the renewed rise in protein use may be linked to adipose tissue shrinking below a threshold at which it can no longer sustain sufficient fatty acid output, and they state that the mechanism remains to be elucidated.

These data matter because they turn “reserve size decides sparing” from a qualitative trend into a quantitative relationship that can be compared across reserve levels. They also hint that reserve size is not the only factor determining how long the sparing phase lasts.

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A larger reserve and a longer sparing phase do not necessarily equate to a more stable ability to spare protein, and a finer study is needed to qualify this. Cherel et al. compared obese Zucker rats (*Rattus norvegicus*) with lean ones and found the sparing phase in obese animals was indeed nine times longer and their daily urinary nitrogen three times lower, yet at the end of the experiment total protein loss in the obese rats was in fact greater (57% against 29% in the lean rats, though the two groups are compared after fasts differing about ninefold in length), because the sparing phase had been stretched too far: while fat was not yet used up, protein had already piled up a larger absolute loss through slow, long-lasting drainage [7]. From this, the authors propose that in extremely obese individuals, a fatal loss of protein may happen before the fat store is exhausted. In contrast, survival time in lean individuals depends more directly on the amount of fat available as fuel. An increase in reserve capacity thus does not raise the chance of survival in a simple linear way.

Dulloo and Jacquet, working on human semi-starvation data, introduce the concept of a "protein energy reserve" (rp), the fraction of lean mass whose protein can be spent as an energy store without endangering life; because it varies independently of body-fat percentage, rp offers a potentially useful cross-species indicator for comparing the efficiency of protein sparing [8]. This concept is not further developed in the present review, but it points to a source of variation that is not captured by reserve size alone.

Following the rule above, when non-protein reserve capacity approaches zero, the sparing mechanism should fail or be strongly compressed. Cephalopods such as the cuttlefish, Sepia officinalis, offer a natural experiment at this boundary. Their tissues contain very little carbohydrate and fat, and their rate of protein synthesis is already high. Once food is withdrawn, the first change in the mantle muscle is a fall in protein synthesis. At the same time, indices of degradation rise clearly only in severely starved animals, with muscle protein burned directly as fuel [9].

3.2 Effects of Tissue Specificity and Timing: Residual Divergence at the Same Level of Reserve

Reserve capacity may explain part of the variation among species, but it cannot explain why species with similar reserves still differ in sparing efficiency. Two further independent comparison dimensions should be considered: tissue specificity (whether sparing is selectively distributed across organs) and timing (at which stage of a fast, sparing is engaged). On tissue specificity, a study of starvation metabolism in the teleost Seriola lalandi gives an example: using fatty acid composition together with compound-specific stable isotope analysis of amino acids, the authors found that the isotopic signal of amino acids in skeletal muscle changed little over 35 days of sub-lethal starvation, and from this they inferred that muscle protein turned over slowly and its structure was relatively protected, while the liver kept taking part in redistributing amino acids [10]. It should be noted that the study did not directly measure rates of protein synthesis or degradation. Hence, the muscle–liver contrast is a reading derived by the authors from isotope data. If that reading holds, this sparing strategy is not a whole-body, undifferentiated metabolic depression, but a way of giving up renewable protein turnover in exchange for keeping structural proteins that cannot be rebuilt, or are hard to rebuild.

On timing, a short-term fasting study in the carp (*Cyprinus carpio*) provides within-species temporal evidence: after three days, the muscle relies mainly on antioxidant defense to handle rising ROS, and by day seven, once antioxidant capacity is overwhelmed, ROS-triggered autophagy is enhanced, and muscle protein begins to be degraded [11]. Because this is a single species sampled at two time points within one short fast, it shows a temporal switch between protecting and degrading protein in that species, not that different fish species follow different temporal strategies; whether temporal specialization of protein protection is general within fish awaits a cross-species comparison made with one common indicator.

3.3 Divergent Molecular Routes in Extreme Phenotypes: Direct, Indirect, and Correlational Evidence

In nature, many kinds of organisms have evolved dormancy to deal with habitats that force extreme fasting. Hibernating mammals and long-aestivating amphibians both reach very strong protein sparing, but the molecular routes behind the effect are not the same. The evidence below is best read in three layers rather than as a single set of "molecular routes": direct protein-turnover evidence (protein measured directly), indirect energy-metabolism evidence (respiration or metabolite measurements from which sparing is inferred), and correlational evidence (parallel changes from which a mechanistic link is proposed).

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The ground squirrel, Ictidomys tridecemlineatus, is a typical hibernating mammal. What was directly measured in the study was the activity of SQR, the enzyme responsible for the oxidative removal of H2S, and the effect of accumulated H2S on respiration in isolated liver mitochondria; protein sparing itself was not measured [12]. The activity of SQR drops markedly during deep cold torpor, so H2S accumulates in the liver and inhibits complex IV in isolated liver mitochondria, from which the authors propose a model in which the accumulation of H2S takes part in the metabolic depression of hibernation; the background figure of about 95% reduction in overall metabolic rate is quoted from earlier work. This should be read as an indirect inference via a mechanism: respiratory inhibition is proposed as a route that could contribute to metabolic depression, but it should not be equated with a direct reduction in protein breakdown in the absence of protein turnover data.

The *Cyclorana alboguttata* gets through the dry season by aestivating. Over six to nine months of aestivation, the oxidative fibers of the cruralis atrophy by about 28%, yet maximal contractile force shows no significant decline and endurance is only mildly impaired. Protection of protein structure is therefore selective. Total antioxidant defense, meanwhile, is maintained at control levels throughout aestivation, and the researchers infer that this may help slow the accumulation of oxidative damage in static muscle protein, which would partly explain why atrophy can be kept within a range that spares protein without impairing its function [13].

Taken together, the H2S mechanism in *I. tridecemlineatus* and the selective muscle protection in C. alboguttata may contribute to a similar protein-sparing phenotype under extreme metabolic depression: to achieve one effect, different lineages may have locked onto distinct upstream regulatory nodes. It should be noted, however, that the fasting state, the tissue examined, and the outcome indicators of the two studies are not directly comparable, so this is a suggestive parallel rather than a demonstrated convergence.

4. Potential Links Between Oxidative Stress and Protein-sparing Strategies: Evidence and Limitations

Most of the evidence linking ROS to protein sparing comes from cell-based experiments or indirect correlations, so the links reviewed below should be read as potential rather than established. The conserved-signaling and divergent-execution aspects are presented together, followed by their limitations.

4.1 Evidence

Early in fasting, the organism breaks down glycogen and then mobilizes fat for fuel. The level of reactive oxygen species (ROS) inside cells shifts with this process, resulting in a mild “oxidative stress” signal. The signal can activate AMPK and inhibit the mTOR pathway, thereby affecting protein metabolism. At the cellular level, studies have directly observed that H2O2 induces phosphorylation and activation of AMPK, after which downstream targets of mTORC1 are dephosphorylated [14]. This ROS–AMPK/mTOR coupling still lacks broad enough comparative evidence across species.

The transcription factor Nrf2 receives the ROS signal and translates it into downstream responses, providing a defense against oxidative stress; within Bilateria, this function has been conserved widely through homologous proteins. SKN-1 in the nematode (*Caenorhabditis elegans)* is the functional homolog of Nrf2, and the two show conservation of this core oxidative stress defense across an extremely long evolutionary distance [15]. Nrf2/SKN-1 can thus serve as an intermediate node linking molecular mechanisms to animal phenotypes. Take the analysis of the *I. tridecemlineatus* study in 3.3 as an example. The paper notes that H2S-sensitive Nrf2 expression is upregulated in the liver during hibernation and suggests that Nrf2 may help regulate SQR expression, which could represent an upstream step in the metabolic depression described in 3.3 [12].

Once the signal is activated, it can affect two kinds of downstream processes: adjustment of antioxidant gene expression and control of protein synthesis and degradation by the AMPK/mTOR axis mentioned above. Whether the two read the same upstream ROS-sensing step remains unsettled by direct evidence. On the other side, the machinery that carries out protein degradation is also called upon in distant groups: after food is withdrawn from the common cuttlefish *S. officinalis*, indices of the ubiquitin-proteasome system in mantle muscle (such as 20S proteasome activity and the level of polyubiquitinated protein), rise together with

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lysosomal cathepsin activity [9]. These pathways show similarities to those in mammalian cells, but the extent to which downstream execution is conserved remains unsupported by direct comparative evidence.

4.2 Divergent Execution

Although upstream sensing is relatively conserved, downstream responses still clearly diverge at the species and tissue levels. Section 3.3 already showed the inference researchers made about *C. alboguttata* [13].

The C. elegans study cited above is best used to illustrate the heterogeneity of ROS indicators rather than as evidence for a protein-sparing mechanism. A recent study of redox state in various tissues and organelles of C. elegans under fasting and refeeding yielded an unexpected result: when measured with an H2O2 sensor, the oxidation level of most cellular compartments dropped during fasting, while the muscle mitochondrial compartment rose [16]. The direction and strength of the ROS response to fasting are thus not uniform across tissues or species; they also depend on the indicator chosen and are hard to fit into a single linear model. This heterogeneity limits how far different studies can be compared and partly explains why opposite ROS directions are reported for different tissues within the same organism.

4.3 A Trade-off Hypothesis

Taking the evidence of 4.1 and 4.2 together, a hypothesis more precise than “ROS affects protein sparing” can be proposed: the upstream ROS-sensing pathway, with Nrf2/SKN-1 as its core node, is functionally conserved on a cross-species evolutionary scale, and the downstream machinery of protein degradation such as the UPS shows similar conservation, but how exactly the two are coupled, and how well the coupling works, still depends on how a given species' pattern of ROS exposure matches its antioxidant buffering capacity. ROS and protein sparing are more likely to be a trade-off than a simple protective synergy. Looking across evolutionary lineages, what is conserved tends to be the sensing machinery at the top, while how the trade-off and coupling are worked out is determined by the ecology and physiology of each lineage. How this relation behaves systematically across wider lineages remains a blank that has not been tested properly, and it is the core question this paper leaves to future comparative physiology.

5. Conclusion

Within Bilateria, protein-sparing during fasting constitutes a composite rather than a unitary adaptive trait, organized into two functional tiers with distinct evolutionary signatures. Upstream regulatory logic that determines whether protein sparing is deployed exhibits strong evolutionary conservation, shared across deeply divergent bilaterian lineages. By contrast, downstream execution — including the magnitude of protein preservation, tissue-specific protection patterns, and the underlying molecular cascades — shows considerable interspecific divergence. Such phenotypic variation is shaped by lineage-specific traits such as energy-storage architecture, tissue-differentiation complexity, and habitat-imposed selective pressures.

Oxidative-stress signaling interacts with protein-sparing within the same “conserved upstream sensing, divergent downstream response” framework. Nevertheless, empirical evidence supporting this coupling remains fragmented across taxa, and the putative trade-off between ROS signaling and protein-sparing has yet to be rigorously validated.

Evolutionarily, fasting-induced protein-sparing represents a natural adaptive solution for optimizing nitrogen resource utilization under amino-acid limitation. While animal fasting physiology can provide conceptual inspiration for engineered nitrogen-use optimization in protein-production biotechnologies, practical translational potential remains unsubstantiated by experimental evidence.

Given these knowledge gaps, a high-priority future research direction within comparative evolutionary physiology is to quantify the strength of coupling between ROS signaling and protein-sparing across phylogenetically broad bilaterian taxa. This can be achieved via standardized molecular readouts, for instance, simultaneous quantification of Nrf2/SKN-1 pathway activation and tissue-specific protein-degradation rates across diverse species.

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