

# HUMAN METABOLIC DOWNREGULATION FOR GENERAL STRESS & 0-G TOLERANCE: (PRELIMINARY) PROOF-OF-CONCEPT EXPERIMENTS

## Jungle Innovations

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### ABSTRACT

Metabolism powers & sustains life, & chronic gravitational unloading tolerance, e.g., weightlessness, is reduced, in part, because terrestrial life typically only experiences 1-G<sub>⊕</sub> loading or more; considerable 1-G<sub>⊕</sub> unloading can occur via aquatic venturing. Larger animals, however, are subjected to a much greater, mass-related counter-gravity metabolic cost (CGMC), more specifically, enzyme-driven *mass* action, *the stuff that makes life animated*, so that removing this component to the metabolic burden bottom-line leads to substantial desynchrony between the various metabolic reactions, as indicated by the rate-of-living life-equation.<sup>1-6</sup> According to the basic, *fundamental*, earthly life metabolic rate-of-living life-equation, on Earth, CGMC<sub>1-G<sub>⊕</sub></sub> contributes ~35% & ~10% to the minimum existential or basal metabolic rate (BMR) of a 100-kg human & 10-g mouse, respectively. This is due to the absolutely greater enzyme *mass-load* that comes with increased size; the non-linear discrepancy is due to the lower pound-for-pound or mass-specific metabolic rate (MR<sub>S</sub>) of larger animals, here reduced to 1/12<sup>th</sup>, even though gravitational forces acts on each unit of flesh-mass & scales directly with gravitational force, which should otherwise result in a 10,000-fold difference. Furthermore, because elapsed (metabolic) time is the just the inverse of MR per unit mass, a time-dose tolerance effect manifests, so that prolonged off-nominal exposure results in progressively greater desynchrony between the various, many metabolic *clocks* & thus, unsurprisingly resulting in dysfunction & pathological manifestations.<sup>7-8</sup> However, it is known that animals in torpor, i.e., sub-BMR states, can be rendered effectively *immune* to even far-off 1-G<sub>⊕</sub>, very large ones too, e.g., hibernating bears tolerate months of near-complete inactivity, considered a natural biomedical model of chronically protected gravitational unloading. Torpid states can so profoundly slow metabolic activity & thus, biological times that animals suddenly appear as if metabolically *down-sized & suspended in time*, & thus more immune. Indeed, many key pathways are temporarily uncoupled, *broken*, or remodeled for greater protection, others are upregulated by the off-nominal exposure, e.g., cold-shock proteins.<sup>9</sup> This is not altogether unsurprising, since the best way to protect a machine, especially a complicated *metabolic machine* is to temporarily & Lego-like disassemble it. Metabolic depression also results in some (variable) core-body cooling even in large hibernators, which in itself boosts tolerance since MR largely depends on temperature. For example, human +G<sub>z</sub>-tolerance, which is poorly tolerated, decreases by as much as 30-40% for a mere degree increase in core-body temperature, equivalent to a ~5-7% increase in MR; cooling reverse it.<sup>10</sup> Yet, a 100-kg hibernating bear downregulates MR to ~30% BMR with no more than 3-4°C of core-cooling, i.e., temperature-independent effects are at play, suggesting a large, untapped, off-nominal tolerance potential.<sup>11-13</sup> And, since torpor is expressed in an extremely varied range of mammals & known to confer unmatched-enhanced tolerance of a myriad of other major metabolic stressors, e.g., extreme acceleration/deceleration, thirst, starvation, isolation, confinement, inactivity, infection, intoxication (e.g., hypercapnia/oxia), hypoxia, hypo/hyperthermia, ionizing-radiation, darkness, decompression-illness, even time itself, if humans could express this state they might similarly manifest broad-spectrum biomedical protection, i.e., *game-changer*.<sup>14</sup> Interestingly, because the CGMC contribution to the metabolic bottom-line in torpor expands vis-à-vis the thermoregulatory burden, 0-G should result in the most profound torpor. This means it may be possible to *completely* offset any lingering adverse effect of weightlessness in large animals, like humans, & transform it into a novel space-life-support resource, to maximize (time-dependent) biological shielding & conservation of resource, i.e., vital given the extreme & austere nature of the environment. As to how one might access this enigmatic state-of-nature, however, remains a centuries-elusive grand-mystery.<sup>15</sup> Interestingly, the lowly MR & other vitals of hibernating bears stands on par with that of similar sized breath-hold diving seals, an environment in which the CGMC is near-collapsed. Indeed, bears frequently hold their breath for minutes-long in hibernation, leading some to suggest that *“the bear may ‘dive’ into hibernation”*, so that this strategy might be the long-suspected pathway that opens-up the possibility of bear-like sustaining this state.<sup>12,16-</sup>  
<sup>20</sup> Though any human, seal-like, down-powered metabolic capabilities are considered *“myth”*, presented here, experimental outcomes of just this capability of some human divers.<sup>21-25</sup> Revealed here, seal-like down-powered metabolic capabilities of human breath-hold divers, specifically, a telltale constellation

of classic physiological hallmarks that typify this state: spontaneous, ultra-fast & profound reversible temperature-dependent/independent sub-BMR with core-body cooling. Current experiments are currently geared towards determining the lowest rate that the metabolic flame can burn at & how just how long it can be sustained in this animalesque state.

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