Hormones, hormesis, and holistic obesity care

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Abstract

Hormones and hormesis are different words, derived from the same root, hormao (to excite). Hormones are chemical messengers which ensure inter-organ and inter-cellular homeostatic communication. Hormesis is the phenomenon in which exposure to low dose of stressor causes a beneficial response, while higher doses have a neutral or negative effect on functioning of the organism. Hormesis is a well-accepted part of plant and animal biology, as well as certain fields of medicine. This commentary describes how obesity related hormones and hormesis are linked, using examples from reproductive endocrinology, bone health and diabetes, to simplify the concept.

Keywords: Endocrinology, homeostasis, metabolic set point, obesity

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Introduction

Hormones are the messengers of health, which convey information between various organ systems and cells, ensuring seamless communication and homeostasis.[1] Hormesis, derived from the same root (hormao, to excite) is a biological phenomenon where exposure to a low dose of stressor (behavioural or chemical) leads to an adaptive, beneficial response, strengthening the individual, though a higher dose of the same stress causes a negative, maladaptive cascade.[2] This biphasic dose-response curve, which may be U-shaped or J-shaped, serves a physiological purpose. It activates protective mechanisms which enhance coping mechanisms and promote resilience.

Hormesis dose responses have been proven to be mediated by specific mechanisms, involving well-characterized transmitters and receptors. These findings support the hypothesis of biological plasticity. They have found wide utility in plant biology and veterinary medicine, and their application in medicine is increasing gradually, especially in gerontology and toxicology.[3]

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Hormesis in lifestyle

Endocrinology and metabolism are a relatively recent entrant to the potential of hormesis. Hormesis and hormones are linked not only by linguistic etymology, but also by physiology, pathology and pharmacology. The concept of hormesis explains various paradoxical situations that are frequently encountered in endocrinology. Diet, exercise, nutraceuticals and physical stress are some non-pharmacological triggers of a protective hormetic response

Exercise is considered therapeutic intervention for various lifestyle and endocrine disorders. In moderation, exercise leads to the release of heat shock proteins which enhance metabolic health. In excess, however, exercise can cause side effects such as myopathy, dehydration and musculoskeletal injury.[4]

Calorie restriction is known to improve longevity. If practiced within moderation, nutrient restriction leads to mitochondrial hormesis. It modulates reactive oxygen species generation in while and beige adipocytes, activates Fox 01 transcription factor, upregulates oxidative phosphorylation genes and mitochondrial stress defensive proteins. These changes increase the metabolic efficiency of mitochondria, thus enhancing cell survival. If the "dose" of calorie restriction is increased, however, malnutrition and its associated complications ensue.[5]

Short term or intermittent hypoxia is also known to be a hermetic influence. Exposure to mild hypoxia enhances vascular nitric oxide storage capacity, and attenuates endothelial dysfunction. Chronic hypoxia, on the other hand, exacerbates insulin resistance and glucose intolerance in obesity models. Metformin as a calorie restriction memetic increases mROS production. This triggers adaptive, pro-longevity pathways such as upregulation of acyl-CoA dehydrogenase-1.[6]

Quantum endocrinology

Conventionally endocrinology has followed the laws of Newtonian physics, viewing physiology in terms of linear feedback. Enhanced understanding of homeostasis, has facilitated acknowledgement of the quantum nature of endocrine dynamics.[7] This has been spurred by the sudden increase in endocrine-metabolic disease burden, with its multitude of clinical presentations. Development of newer drugs, designed to improve endocrine-metabolic health, and realization of person-specific responses, has also contributed to this.

Rebound responses

The simplest example of hormesis in endocrinology, perhaps, is the role of glucose-lowering drugs such as insulin and sulfonylureas, used in appropriate doses, they lead to euglycaemia. In higher doses, they can cause hypoglycaemia, which may lead to rebound hyperglycaemia (the Somogyi phenomenon).[8] While not a "purist" exemplar of hormesis, this appraisal sets a benchmark for the appreciation of hermetic endocrine interventions.

Yet another paradox is the effect of parathyroid hormone (PTH). Administered intermittently, it stimulates osteoblastic activity and supports bone formation. It given continuously, however, PTH has an osteoclastic, or bone-resorbing effect.[9]

Another example from reproductive endocrinology is that of testosterone. Used in appropriate doses, it leads to required benefits. Given in higher doses, however, it may cause paradoxical worsening of symptoms. A similar situation is noted with exposure improves quality of life, while excessive use of pornographic graded exposure improves quality of life, while excessive use of pornographic stimuli may lead to sexual dysfunction.[10]

Xenohormesis

Xenohormesis is the term given to the effects of dietary polyphenols on obesity. Resveratrol, in lower doses, increases energy expenditure and exhibits an anti-inflammatory effect. These advantages are not seen in high-dose supplementation.[11] Berberine is another example of xenohormesis. It activates the AMPK/SIRT 1 pathway, thus encouraging adipose tissue remodeling, thermogenesis and UCP-1 expression, while retarding differentiation and proliferation of adipocytes.

Obesity management

Newer drugs, such as glucagon-like peptide 1 receptor agonists (GLP1RA), exhibit a pharmacological peptide paradox. Used at lower doses to treat diabetes or hyperglycaemia, higher doses are able to manage obesity without causing hypoglycaemia. This suggests a hormetic response of sorts. Basic research, however, demonstrates that GLP1RA, act via non-hormetic responses. Their dose-dependent response curve, regarding weight loss, is non-hormetic while glucose-lowering effect plateaus at higher doses.[12]

The hormetic threshold

It is the overall management of obesity, however, that the principles of hormesis operate. The metabolic set point is a notoriously stubborn barrier to cross.[13] Using "high dose" interventions of dietary restriction, exercise or drugs may have a visible short term benefit. Maintaining and sustaining this in the long term, though, is extremely difficult. Most people who achieve sudden weight loss find it difficult to maintain, and may end up giving more weight (the rebound phenomenon) (personal communication: The law of more than equal and opposite reaction). Application of the principles of hormesis helps overcome this challenge.

Introducing low intensity changes, whether pharmacological or lifestyle-based, designed to achieve low level increments in weight loss and metabolic health, allow accomplishment of sustainable, sufficient weight management in the long-term. Individuals who live with obesity, and are impatient with results, may be counselled about hormesis as a homeostatic mechanism, designed to break habitual and hedonistic feedback loops. Examples that we use in the clinic include likening weight loss medication to salt, pepper and spice: low doses are stimulatory, while higher doses cannot be tolerated.

Being future fit

Hormones are age-old molecules, while hormesis has a relatively young history of discovery by plant biologists. Initially, the concept was shunned by medicine because of its similarity to homoeopathy. In recent decades, however, hormesis has gained the attention of clinicians and researchers alike. Endocrinology with its vast library of hormones, neurotransmitters and hormonoids,[14] is a perfect ground for the exploration of hermetic phenomena. In both health and disease in pharmacology, hormesis has an important role to play. Continued discussion and debate, conducted in the spirit of science, will help uncover more and more applications of hormesis. These will help expand our education and learning, as well as enhance the efficacy and efficiency of our clinical care.

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