REVIEW ARTICLE

Are you feeling comfortable? – Measuring Clinical Hormesis

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Abstract

Hormesis is a biological phenomenon where exposure to a low dose of a stressor or toxin induces a beneficial adaptive response, whereas higher doses may have detrimental effects. The concept of hormesis is being increasingly appreciated not only in toxicology and in pharmacology, but also in nutrition, clinical medicine, and in situations involving everyday life. Hormesis is an adaptive response of cells and organisms to a moderate and intermittent stressful stimulation. Following such stimulation, the organism must respond, and it has to make a choice: either treat it as a positive ‘challenge’, adapting to it and increasing its robustness, or treat it as a negative ‘threat’ with detrimental consequences for physiology and health. In clinical and everyday situations it is usually difficult to advise patients on how to determine the strength of such stimulation, and when to decide that each new stimulation is too low (ineffective), moderate (appropriate for health), or excessive (damaging to health). In this paper we argue that it is possible to rely on the subjective feelings of ‘comfort vs discomfort’, for deciding about the strength of the stimulus: if each exposure to a stimulation is felt by the individual as a ’comfortable’ event, then it is likely that its effects are beneficial (a hormetic challenge). If it is felt as an ‘uncomfortable’ event, then it is likely that it is damaging to health (a threat). These feelings take place in the anterior insula which evaluates the state of resources for responding to an external or internal event, and are a result of the integration of signals from the amygdala, hippocampus, and the prefrontal cortex.Nutritional hormesis, and digital cognitive stimulation are mentioned as two examples.

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Highlights

- A stressor is beneficial when it is ‘hormetic’ - not excessive and not insufficient
- The organism must decide whether to treat this stressor as a challenge or a threat
- If we feel comfortable with a stressor, we are perceiving it as a beneficial challenge
- If we feel uncomfortable with a stressor, we are perceiving it as a damaging threat
- Comfort/discomfort is the result of integration of signals in the insula, amygdala, etc.

1. Introduction

In many situations in nature it is possible to observe the phenomenon of hormesis, a dose-response relationship, where exposure to a low or moderate dose of any stressor or toxin (i.e. a challenge) has a beneficial effect on an organism, while higher doses of the same stressor may disturb homeostasis and result in damage of the organism. Hormesis is characterized by a U-shaped or J-shaped curve, where low doses have near-negligible effects, moderate doses are stimulatory or adaptive, and high doses are detrimental [1]. The notion of hormesis does not assume that all stimuli or substances have a linear dose-response relationship. In other words, hormesis challenges the linear model where the more we increase the dose, the more the benefit. Instead, hormesis suggests that some stressors, within a certain range of exposure, can stimulate adaptive responses that enhance resilience and promote health. A stressful challenge stimulates the organism’s stress response pathways with the aim to mount adaptive actions involving cellular and tissue repair mechanisms [2].

However, the specific dose range, the ‘hormetic window’, for positive effects can vary among different stressors and individuals. It is necessary to ensure that the stressors are applied within a safe and beneficial range [3]. A challenge that matches our skills and abilities causes well-being. If the challenge is above our abilities then it causes negative feelings (tiredness, lack of energy, anxiety etc). If it is below our abilities, it causes boredom or under-stimulation. It is important therefore to know when the exposure to each new stimulus is appropriate for our needs. Anything less or more than this range of exposure, does not invoke a positive hormetic response. Some classic examples of hormesis are summarized in Table 1.

Table 1. Examples of hormetic stressors.

Type of challenge	Effect	Molecular mechanisms
Physical exercise [4].	Moderate exercise improves cardiovascular and respiratory parameters, enhances metabolic function, and is beneficial to cognition and memory. On the other hand, excessive or intense exercise can lead to damage, while no exercise at all is also detrimental to health.	Upregulates PGC-1α, Nrf2, and Vascular Endothelial Growth Factor (VEGF). Improves IL-6, inhibits TNF-α, and stimulates glucose uptake.
		CR improves HSP-70, upregulates

Caloric restriction [5].	Limiting calorie intake, such as caloric restriction (CR) and intermittent fasting, has several positive effects on lifespan and health in various organisms, including humans. On the other hand, excessive or prolonged caloric restriction has negative results.	cytoprotective antioxidants (vitamin E, coenzyme Q10), membrane redox enzyme activities in neurons, mitochondrial oxidative phosphorylation, glycolysis, and NAD/NADH metabolism.
Cognitive hormesis [6][7] (including an influx of digital information that requires action) [8].	Mild stressful brain stimulation upregulates neuronal defense and repair pathways. It enhances vision, immune function, wound healing, muscle strength, inflammatory response, as well as social and emotional functioning. Excessive mental effort carries negative effects such as stress and anxiety.	Cortisol modulation, regulation of mineralocorticoid and glucocorticoid receptors, among others. Activates the neuronal stress response.
Radiation Therapy [9].	The principle of hormesis is considered when determining the appropriate dose, aiming to maximize the therapeutic effect on cancer cells while minimizing damage to healthy tissues.	Regulation of antioxidant molecules, repair of DNA damage, p53-related apoptosis, cytokine-regulated auxiliary apoptosis, and suppression of inflammatory markers.
Nutritional Hormetins [10].	These are compounds which invoke hormesis, such as flavonoids, polyphenols, kinetin, fisetin, curcumin etc.	Enhanced stress response and heat shock protein actions, autophagy, DNA damage repair, sirtuin activation and regulated inflammatory response.
Heat Stress [11].	Controlled exposure to heat stress, such as saunas or hot baths, improves cardiovascular function and other physiological functions. Disproportionate heat stress, on the other hand, can lead to heat-related illnesses.	Regulates heat-shock proteins, immune function, cell signaling, cell-cycle regulation, and proteome homeostasis. Modulates Nrf2, IL-6 and IL-10.
Social hormesis [12][13].	Personal and virtual social activities reduce social isolation, improve well-being and quality of life.	Improved function of hippocampus and dendritic/synaptic efficiency among others.
Sexual hormesis [14].	Erotic stimulation benefits several domains such as the endocrine, immune, circulatory and neurological systems.	Improves oxytocin (with corresponding cardiac benefits), autophagy, estrogen and testosterone concentration.

2. Discussion: Challenge vs Threat

Following an exposure to a stimulus (physical, nutritional, cognitive, emotional etc.) the organism has to select whether to treat this new experience as a challenge or as a threat [15]. In other words, exposure to a stimulus can be positive

(challenge) or negative (threat) [16]. A challenge is perceived when the available resources meet or exceed demands, whereas threat is perceived when demands surpass available resources [17]. After a stimulus has been defined as a challenge or as a threat, there are several physiological responses (Table 2).

Table 2. Some physiological changes which occur in the presence of a challenge or threat [18][19].

Challenge	Threat
Increased sympathetic-adreno-medullary activity (SAM), - fast acting.	Increased SAM activity and increased pituitary-adreno-cortical activity, - both slow acting.
Mobilization of energy for action.	Activation of a “distress system”.
Activation of oxytocin and neuropeptide Y, secretion of catecholamine.	Cortisol release.
Release of neurotransmitters such as serotonin and endorphins, contributing to an improved mood and a sense of well-being.	Symptoms of anxiety, excessive stress.
Increased heart rate and cardiac output.	Increased heart rate and a small increase or stabilization of cardiac output.
Increased blood flow to the brain and muscles.	Blood flow to the brain and muscles is not increased.
Increase of blood glucose, and fatty acid concentration, in order to be used as fuel for addressing the challenge.	Efficiency of energy use is reduced. The mobilization of usable energy is slower than in a ‘challenge’ state.
Facilitates decision-making, effective cognitive function, efficient self-regulation, and increased anaerobic power.	Ineffective decision-making and cognitive function, inefficient self-regulation, and decreased anaerobic power. The stress response can impact cognitive functions such as memory, attention, and decision-making.
The organism adapts to the stimulus and becomes more robust.	The organism does not adapt, and is left damaged from the event.

3. Evaluation

In everyday life it is not possible to measure exactly the limits between too much, enough, or too little exposure to an event. Nor it is necessary to resort to artificial or mechanical measurements. Our body has its own evaluation mechanisms which can assist. These mechanisms are able to differentiate when we are within our comfort zone, or when we are about to exit it. The mechanisms evaluate sudden and unexpected problems and can ‘judge’ whether we are able to overcome the problem or be overwhelm by it. In other words, we (subconsciously) make a choice between what is a ‘challenge’ and what is a ‘threat’.

If we have the necessary resources to overcome each new stimulation, we consider it as a challenge which requires

action (the hormetic stress response) and during this action the organism becomes resilient and the damage is repaired. A challenge is perceived when there are available coping strategies. If there are no appropriate resources available, if the situation is perceived as leading to failure, then the stimulus is considered as a threat, and our organism takes steps in order to avoid it. ‘Threat’ is not necessarily a threat to our survival, but a damaging event which disturbs our biological balance and which overwhelms any available defense resources of our body. This threat causes negative emotions, such as a sensation of ‘being badly under pressure’, feeling uncomfortable, feeling that it is too much, a distress. These feelings show that the stimulus is not positive any more but it is now becoming negative. On the other hand, when we feel positively challenged, when we are just at the limits of our comfort zone, or we experience a pleasant rousing sensation, all these mean that beneficial hormesis is taking place. Whereas if we feel that we want to do more, and wishing for the experience to increase, this means that there is under-stimulation and that the stimulus can safely be increased.

3.1. Anterior Insula

The main evaluation of ‘challenge vs threat’ takes place in the anterior insula in the brain. The human insular cortex is found within the lateral sulcus or the fissure between the temporal lobe and the parietal/frontal lobes and it is typically subdivided into a posterior and an anterior part [20].

The anterior insula gathers and coordinates signals from a variety of sources. It is connected to the limbic regions, including the amygdala, and integrates autonomic and signals arising peripherally into cognitive and emotional functions [21]. It evaluates signals from the bowel, liver and lungs, the gut microbiome, and other biological signals and sensations based on the existing available energy in order to adapt to the stimulation. The anterior insula integrates these signals and mediates an awareness of the totality of the physiological inputs. Therefore, the subjective feeling of ‘comfort’ or ‘discomfort’ indicates that the person is, or is not, experiencing hormesis, respectively.

3.2. Amygdala

In addition to the anterior insula, during the evaluation of ‘challenge versus threat’, the amygdala plays a significant role. It assesses the emotional significance of a stimulus and it plays a part in determining the potential threat level of each situation [22]. The amygdala receives input from various sensory organs, such as the eyes, ears, and other sensory pathways. These inputs convey information regarding the external environment, including potential threats or challenges. It is capable of a quick and automatic assessment of the emotional significance of stimuli. It processes information regarding the stimulus and evaluates whether it is associated with danger, fear, or a potential challenge. If a stimulus is associated with a previous experience that was emotionally significant (for example, fear) or threatening, the amygdala can trigger a faster and more intense emotional response based on that past experience. The amygdala is well-connected with other regions of the brain, including the prefrontal cortex, hippocampus, and the hypothalamus. These connections allow the amygdala to influence cognitive processes, memory, behavioural response, and the physiological events associated with the stress response. If the amygdala perceives a stimulus as a threat, it can activate the body's stress response, leading to physiological changes associated with the ‘fight-or-flight’ reaction.

However, the amygdala's assessment is not always accurate, and it can sometimes lead to false alarms or overreactions. Additionally, the prefrontal cortex and hippocampus play roles in contextualizing and fine-tuning the amygdala's responses, providing a more nuanced and reasoned evaluation of stimuli. The amygdala's ability to quickly assess emotional significance is an evolutionary adaptation that helps organisms respond rapidly to potential threats in their environment, contributing to survival.

The amygdala and anterior insula are interconnected and communicate reciprocally as part of the broader neural circuitry involved in emotional processing and stress response. While the anterior insula might contribute to assessing the internal physiological state of the organism, it is the amygdala that provides a more accurate threat assessment.

3.3. Hippocampus

In addition, the experience is integrated within the realm of memory, where the hippocampus assesses the relevance of this new experience comparing it to past experiences. If the brain perceives a situation as a threat, it activates the sympathetic nervous system, leading to the release of stress hormones (adrenaline and noradrenaline) from the adrenal glands. Instead, if the situation is perceived as a challenge, there is subsequent activation of adaptive mechanisms which make the individual better able to cope with future stresses.

The hippocampus also takes part in this process. The hippocampal synaptic plasticity is enhanced following signals from the amygdala. It is, in other words, a hormetic response, although prolonged and elevated levels of stress cause inhibition of the hippocampal function [23]. Individual responses to comfort can vary, and factors such as personal experiences, cultural background, and personality traits can influence how someone perceives and physiologically responds to a new event. Additionally, comfort is a subjective experience that encompasses both physiological and psychological components, reflecting a sense of safety, ability to cope, and positive emotional states.

These physiological responses are part of the body's evolutionary adaptation to respond to perceived threats. While they are essential for survival in acute situations, chronic activation of the stress response can have negative consequences for both physical and mental health. Recognizing and managing discomfort in new situations is important for promoting well-being and mitigating the potential negative effects of chronic stress

4. An example of hormetic challenge

In today’s technological environment, Digital Information-That-Requires Action (DITRA), may be considered as a hormetic stimulus, and the organism has to decide whether exposure to such information leads to a beneficial consequences to the organism or if it is detrimental (threat, addiction). Digitally-derived Information that requires a response is being transmitted from external sources (internet, smartphones etc.) to the brain much faster and much more frequently in a modern environment, and places an additional burden on our brain and cognitive processes. It is likely that as technology progresses, the exposure to such stimulation will increase significantly and we need to adapt to this. Following exposure to DITRA, there is activation of the neuronal stress response with changes in the expression of transcription factors,

microRNAs and other factors which regulate stress resistance and adaptation [8]. There is also alteration of synaptic plasticity, modulation of Mitogen-activated protein (MAP) kinases, Insulin/IGF-1 signaling and many others [24]. The danger exists that overexposure to DITRA will lead to brain fog, anxiety, depression, addiction [25], and other adverse effects, and therefore it is imperative to rely on innate mechanisms which signal that the experience is comfortable (challenge) or that it is uncomfortable (threat).

5. Conclusions

Hormesis, the physiological dose-response process, aims to help the organism adapt to external and internal stimulation and emerge more resilient after each event. As a crude measure of the magnitude of the simulation it is possible to rely on subjective feelings which are based on concrete physiological basis in the estimation of the event. Feeling ‘comfortable’ indicates that the body is perceiving the stimulation as a rousing challenge. Feeling ‘uncomfortable’ means it is perceiving it as a damaging threat. It is relevant to highlight that the terms ‘discomfort’ and ‘uncomfortable’ are often used interchangeably, and they share similarities in meaning, but there can be nuanced differences in certain contexts. Generally, both terms describe a state of unease, lack of comfort, or a sense of physical or emotional disturbance. This state of ease or unease is not only applicable to emotions, but it can also reflect biochemical hormesis, when internal exposure to toxins, nutrients, or other stimulants may disturb homoeostasis which, in turn, initiates positive or negative signals to the nervous system.

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