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COMMENTARY

Commentary on "Neg-entropy is the true drug target for chronic diseases"

KEY WORDS

Neg-entropy;
Drug target;
Chronic diseases

In this issue of *Acta Pharmaceutica Sinica B*, Li et al. presented a perspective on drug discovery, proposing the concept of negentropy as a central mechanism for combating chronic diseases. This paper introduces a new therapeutic paradigm, shifting from traditional single-target drug design to a more systemic strategy aimed at restoring biological order through the regulation of entropy. While the proposal is thought-provoking, its practical implications require further exploration and empirical validation. In this commentary, I will discuss the key points of the article, critically evaluate its strengths, and highlight areas that warrant additional attention.

1. The concept of negentropy in drug discovery

The concept of entropy originates from thermodynamics, where it primarily denotes a state of disorder. In an isolated biological system, entropy tends to increase as metabolic dysfunctions, inflammation, infection and cellular damage accumulate over time. The authors propose that chronic diseases arise from entropy-increasing induced disruptions within the body, and that restoring order—negentropy—through regulation of metabolic, immune, and/or cellular mechanisms may offer a therapeutic solution.

This framework challenges the traditional reductionist focusing on single molecular targets and instead underscores the importance of systemic regulation. By introducing the concept of head-goose molecules (HGMs) that orchestrate biological networks, the paper outlines a strategy for drug design that extends beyond interaction with a single protein or pathway. Instead, it aims to reprogram multiple biological axes. For complex chronic conditions such as metabolic syndrome, cardiovascular diseases and cancers, each driven by intertwined metabolic, inflammatory and immunologic disturbances, this system-based approach holds promise for more holistic and effective interventions.

2. Strengths of the approach

A key strength of the perspective lies in its multidisciplinary approach, integrating biology, medicine, pharmaceutics, physics, chemistry, mathematics, materials science, etc. The authors present a compelling argument for multi-target therapies, suggesting that systems-level modulation of complex diseases can be achieved by engaging HGM-piloted multiple pathways. They highlight AMPK, GLP-1R, and SIRT1 as pivotal components within this framework, supported by extensive evidence demonstrating their central roles in metabolism, inflammation and immune regulation. This interconnected perspective captures the intricate nature of biological systems and marks a departure from the conventional, overly reductionist models of disease treatment.

3. Challenges and limitations

While the article presents an exciting conceptual framework, several key challenges must be addressed before the idea of negentropy-based drug discovery can be realized in practice.

1. Measurement and quantification of bio-entropy

One of the most critical challenge lies in operationalizing the concept of negentropy. Although the paper describes how restoring biological order may mitigate disease progression, methods for quantitatively assessing bio-entropy in preclinical or clinical contexts remain unclear. There is therefore an urgent need to develop reliable biomarkers for bio-entropy and negentropy.

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For instance, how can bio-entropy be measured in a patient's body, and how can such metrics be correlated with clinical outcomes?

2. Mechanistic validation of HGMs

The notion of HGMs is conceptually intriguing; however, it is still hard to provide a definitive network mechanism supporting the roles of HGMs in systemic metabolic remodeling. While AMPK, GLP-R, SIRT1, etc. might be effective regulators for metabolism, their function as HGMs to integrate multiple biological processes and cause negentropy effect largely remains theoretical. Experimental validation will be essential to demonstrate how key HGMs modulate multiple pathways concurrently, particularly within chronic disease models.

3. Translational barriers

Significant translational challenges remain in transforming this concept into practical therapies. For example, HTD1801, a novel agent for type 2 diabetes, could be considered a potential negentropy drug, but it's detailed molecular mechanisms remain investigation.

4. Moving forward

To bring the concept of negentropy-based therapies into clinical practice, future research should prioritize several key areas:

1. Development of reliable biomarkers

Establishing biomarkers that accurately reflect a patient's bio-entropy status is essential. Multi-omics approaches, such as metabolomics and proteomics, may be valuable for quantifying biological order at the system level.

2. Experimental validation

Comprehensive preclinical and clinical studies are required to validate the concept of HGMs and confirm their capacity to modulate multiple biological functions.

5. Conclusions

The article offers a novel and visionary framework for drug discovery against chronic diseases, advocating a paradigm shift from single-target to systems-level therapeutic strategies. The concept of negentropy holds considerable promise for addressing complex conditions such as metabolic syndrome, cardiovascular diseases, and cancers. However, translating these ideas into real-world therapies will require substantial mechanistic validation, clinical translatable biomarkers, and relevant regulatory issues. While the work lays a strong foundation for future research, much remains to be explored before negentropy-based drug discovery can be established as a mainstream strategy in practice.

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