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EDITORIAL

Beyond the Brain: The Peripheral Revolution in Neurodegenerative Diseases

Sarwat Jahan[1], Muhammad Ikram[2] and Zeeshan Khan[3]
[1]Department of Pharmacology, Northwest School of Medicine[2] Department of Pharmacology, Institute of Pharmaceutical Sciences, Khyber Medical University,[3] Northwest School of Medicine

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Over the past few decades, it has been generally believed that neurodegenerative diseases are associated with the central nervous system due to the death of neurons, protein accumulation, oxidative stress, and neuroinflammation (1, 2). Therefore, considerable scientific effort has been devoted to the discovery of drugs that can affect the pathogenic processes in the brain. Nevertheless, although a lot of achievements have been made in neuroscience, there are no effective therapies capable of changing the course of the disease since several neuroprotective therapies failed during clinical application (3).

Evidence is piling up to show that neurodegeneration is not just an occurrence that affects the brain but rather a syndrome that arises due to constant interaction between the brain and other peripheral organs (4, 5). In recent years, there has been a trend moving away from the classical view that focuses on the brain towards a systems biology view, where the roles of the gut, liver, kidneys, immune system, vascular system, and metabolic organs are critical for neuronal health and disease (6). These peripheral organs are no longer thought of as secondarily involved when the brain is diseased.

There is a link between the brain and the gut, which stands out among the most convincing theories (7). Gut dysbiosis was associated with the loss of barrier function in the intestine, inflammation, changes in microbial metabolite production, and protein misfolding (8). Indeed, in Parkinson's disease, it has been shown that α-synuclein pathology occurs in the enteric nervous system several years before motor deficit, indicating that some pathological processes may start outside the brain (9). In addition, there are links between diseases linked to liver dysfunction, chronic kidney disease, metabolic diseases, and neuroinflammation with cognitive impairment due to oxidative stress, immune dysfunction, and increased toxicity. However, equally important, it is the fact that the immune system serves as an active link between peripheral tissues and the brain. Peripheral cytokines, immune cells, extracellular vesicles, and metabolic signaling pathways regulate microglia activation and neuroprotection, thus turning neuroinflammation into a systemic process (10).

These discoveries are essential for further translational research in this field. At present, almost all experiments evaluating therapeutic agents by their effect on the brain are performed without much attention to the consequences of such an effect on the peripheral physiology of the organism. The difference between these two effects may be one of the reasons why most of the

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neuroprotective agents that work successfully in animal models show poor results during the phase of clinical trials. Thus, a systems biology approach to neurodegeneration may be vital for successful translation of the results.

In addition, the current landscape of therapeutic strategies is bound to change. In the future, therapeutic regimens will likely switch from being monotherapeutic to more sophisticated treatment protocols, which will include not only the components of immunomodulation, metabolic correction, gut microbiome manipulation, vascular protection, and classical CNS therapy but also elements of neuroprotection (11). On top of this, new approaches such as multi-omics, artificial intelligence, and precision medicine offer a way to discover networks and peripheral biomarkers, which will allow the early diagnosis of the disease and personalize therapy (12). Neurodegenerative diseases are no longer brain disorders but diseases that emerge due to the disruption of biological communications between several organs and systems.

The future of neurodegeneration research can be seen in the transition away from studying neurodegeneration on an organ-by-organ level to looking at the bigger picture of systems biology. Such a shift would entail collaboration between neuroscientists, immunologists, gastroenterologists, heap-tologists, nephrologists, endocrinologists, and computational biologists, all of whom seek to learn more about the effect of organ network function on the brain. By adopting a broader perspective, researchers could discover novel biomarkers and therapeutic targets that would allow them to solve many of the difficulties faced by the neurodegeneration field in the past several decades. To understand neurodegeneration, we must go beyond simply studying the brain and recognize the importance of the rest of the body's health in this process.

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