Editorial

Discovery Medicine 2026; 38(210): 2328–2331
https://doi.org/10.24976/Discov.Med.202638210.182

Pathophysiological Significance and Measurement Methods of Interstitial Fluid pH

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Submitted: 18 May 2026 Accepted: 4 June 2026 Published: 23 July 2026

Blood is a useful and easily obtained fluid that provides important information regarding human health. Furthermore, from the perspective of acid–base balance, which is influenced by acid production resulting from energy metabolism within the body, arterial blood pH is considered critical. The normal range for arterial blood pH is strictly maintained between 7.35 and 7.45. This is because proteins present in the blood, such as hemoglobin (Hb) and albumin, act as powerful pH buffers. On the other hand, with a few exceptions, hormones and neurotransmitters generally exert their physiological activity not in the blood but in the interstitial fluid by binding to their receptors. This occurs because these receptors are generally located on the plasma membrane, with the exception of nuclear receptors such as those for steroid hormones and thyroid hormones. Receptors expressed on the plasma membrane are in contact with the interstitial fluid, which is an extracellular fluid. The structures of these receptors change in response to alterations in the interstitial fluid pH, and the structures of hormones and neurotransmitters also change in response to variations in interstitial fluid pH. Consequently, changes in interstitial fluid pH significantly affect the expression of hormone and neurotransmitter activity. However, obtaining information regarding interstitial fluid pH is difficult. In this editorial, I describe the impact of interstitial fluid pH on hormone activity and explain how interstitial pH can be measured using specific examples.

First, I provide a concrete example of how changes in interstitial fluid pH impact hormonal activity. Insulin facilitates glucose uptake into the intracellular space of muscle cells and adipocytes [1,2,3,4]. The insulin-induced stimulatory effect on glucose uptake has been reported to be diminished by a reduction in pH in the interstitial fluid [1]. Consequently, a diminished interstitial fluid pH contributes to the development of insulin resistance [5]. In patients with type 2 diabetes mellitus (T2DM), glucose metabolism relies primarily on glycolysis because of impaired mitochondrial function [6,7]. Compared with healthy individuals without T2DM who have normal mitochondrial function, individuals with T2DM produce significantly greater amounts of acid (H^+), leading to a decrease in interstitial fluid pH. Thus, the interstitial fluid pH is lower in individuals with T2DM than in healthy individuals without T2DM [8,9,10,11]. This lowered interstitial fluid pH decreases the effects of insulin on glucose uptake [1]. In summary, the reduction in interstitial fluid pH observed in patients with T2DM is believed to contribute to insulin resistance through this decrease in interstitial fluid pH [1].

Patients with T2DM often develop microvascular complications due to hyperglycemia, which can lead to neurological dysfunction and increase the risk of mental disorders such as dementia [12]. Additionally, as a result of the onset of insulin resistance [13,14,15], individuals with T2DM are more likely to develop Alzheimer's disease, a nonmicrovascular form of dementia [13]. Why does insulin resistance lead to Alzheimer's disease? One of the primary contributors to Alzheimer's disease has been reported to be the formation of amyloid-β [16,17], although it remains necessary to consider how the accumulation of amyloid-β directly causes the disease [16,17]. Patients with insulin resistance have high insulin levels in various tissues, including the brain. Insulin acts as a substrate for neprilysin, an enzyme that degrades amyloid-β [18]. Consequently, during a state of insulin resistance marked by elevated insulin levels, neprilysin predominantly metabolizes insulin. This results in the decreased degradation of amyloid-β, consequently leading to its accumulation [18]. This implies that insulin resistance may contribute to the onset of Alzheimer's disease [14]. Additionally, the pH-dependent activities of β- and γ-secretases should be considered. Amyloid-β is produced from amyloid precursor protein by β- and γ-secretases [18,19]. The activities of β- and γ-secretases are heightened by a decreased pH (i.e., under acidic conditions) [20,21,22,23,24,25]. Thus, a reduced interstitial pH results in elevated amyloid-β production [26]. Therefore, the reduced interstitial fluid pH detected in insulin resistance leads to the increased accumulation of amyloid-β by both accelerating its buildup and decreasing its degradation.

Although interstitial fluid pH is crucial for maintaining bodily functions, measuring it is difficult compared with measuring blood pH because of the complexity of obtain-

ing interstitial fluid. Therefore, even though the importance of interstitial fluid pH is widely recognized, virtually no efforts have been made to collect data on interstitial fluid pH and use these data to improve health promotion strategies.

One method for measuring interstitial fluid pH involves the use of ^{31}P nuclear magnetic resonance (NMR). By using ^{31}P NMR, it is possible to quantify creatine phosphate (CrP) and inorganic phosphate (P_i) and to determine their peak positions via magnetic resonance spectroscopy (MRS). The peak position of P_i identified through MRS is influenced by the solution's pH [27]. The chemical shift of the P_i (δ_{P_i}) signal relative to the CrP signal is calculated and plugged into Eqn. 1 to derive the interstitial fluid pH [27].

$$\text{pH} = pK_a + \log \frac{\delta_{P_i} - \delta_a}{\delta_b - \delta_{P_i}} = 6.730 + \log \frac{\delta_{P_i} - 3.275}{5.685 - \delta_{P_i}} \quad (1)$$

pK_a = 6.730

δ_a = The chemical shift of $H_2PO_4^-$ signal relative to the CrP signal, 3.275 ppm for acidic protonated species, $H_2PO_4^-$

δ_b = The chemical shift of HPO_4^{2-} signal relative to the CrP signal, 5.685 ppm for basic protonated species, HPO_4^{2-}

In the extracellular (plasma and interstitial fluid) environment, molecules can move freely because of the low viscosity of the solution [27]. Because molecular motion is rapid, spins are less likely to release energy, resulting in longer relaxation times (RT: the interval between the application of radiofrequency pulses that produce a rotating magnetic field) [27]. On the other hand, in the intracellular (cytoplasmic and organelle) environment, high viscosity and the presence of many macromolecules, such as proteins, make it easier for phosphate ions to bind [27]. Consequently, molecular motion slows down, and spins interact more readily with their surroundings. This makes it easier for energy to be released, resulting in a shorter RT [27]. As noted above, in ^{31}P NMR measurements, the RT of P_i in the extracellular (interstitial) fluid is longer than that of P_i in the intracellular fluid; therefore, to distinguish between extracellular (interstitial) and intracellular P_i signals, the RT is set to 500 ms and 5000 ms, respectively. Specifically, by shortening the RT to 500 ms from 5000 ms, the extracellular (interstitial) P_i signal, which has a longer RT, is reduced. This technique allows researchers to distinguish between extracellular (interstitial) and intracellular P_i signals, enabling the simultaneous measurement of the pH of the interstitial fluid and the intracellular fluid. In this way, we accurately assess the δ_{P_i} of both extracellular (interstitial) and intracellular P_i signals to determine the pH of the intracellular and extracellular (interstitial) fluids using Eqn. 1.

Another method for measuring interstitial fluid pH is conceptually the same as that used for the continuous glucose monitoring [28,29,30,31] and ketone bodies [32]. Specifically, microneedles are transdermally inserted into the interstitial spaces within the subcutaneous tissue, guiding the interstitial fluid to a pH sensor where the pH is measured. The pH sensor used is an ion-sensitive field-effect transistor (ISFET). To verify the accuracy of the pH measurements utilizing these ISFET-equipped microneedles, cross-validation with the pH measurement results obtained via MRS is essential. This method remains in its developmental stages, and further investigation is needed regarding the design of the microneedles and the configuration of the devices, including the ISFET. In addition, measures must be taken to prevent CO_2 in the collected liquid from leaking into the surrounding environment, as this has a significant effect on the pH level.

In summary, while interstitial fluid pH is crucial for maintaining bodily functions, it is not generally used to assess our health condition because of the difficulty and complexity of measuring it. From a pathophysiological perspective, I hope that an increasing number of researchers and clinicians will recognize the importance of interstitial fluid pH in promoting our health, and that data on interstitial fluid pH will contribute to improving human health. I would be pleased if this paper serves as a step toward achieving that goal.

Availability of Data and Materials

Not applicable.

Author Contributions

YM is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the acquisition, analysis, and interpretation of data; the preparation of the manuscript; reading and approving the final version of the manuscript; and for being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

I would like to express my deepest gratitude to all the staff at the Kyoto Industrial Health Association for granting me the opportunity to compose this paper and for their thoughtful consideration.

Funding

This work was supported by grants from Japan Society of the Promotion of Science (JSPS KAKENHI Grant

Numbers JP18H03182, JP21H03368, JP23K21626, and JP26K23743).

Conflict of Interest

Yoshinori Marunaka was a member of the Editorial Board of this journal at the time of acceptance. Yoshinori Marunaka had no involvement in the review of this article and has no access to information regarding its review. Kyoto Industrial Health Association is a general incorporated foundation. As the representative director and the president of this general incorporated foundation, the author has no conflicts of interest whatsoever in relation to the present article.

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