Benefits of post-stress immunosuppression: a viewpoint from exercise immunology

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Abstract In understanding the relationship between exercise and immunity, the “open window theory” is a well-known theory stating that immediately after high intensity exercise, temporary immunosuppression occurs, which increases the risk of infections such as upper respiratory tract infections. Why does such a phenomenon occur? Does immunosuppression after severe exercise have physiological significance? In this paper, we propose a theory of super homeostasis. In other words, we verify that the open window theory is an important biological reaction when trying to understand the reason why we do exercise, more than it is the indispensable physiological response to the whole body.

Keywords: open window theory, TLR, TNF-α

Introduction

It is well known that the Ministry of Health, Labour and Welfare in Japan has been promoting “National Health Promotion Movement in the 21st Century (Health Japan 21)” since 2000. This health promotion movement has set goals in 9 areas (nutrition and dietary habits, physical activities and exercise, rest and mental health development, etc.)1). Thus, “nutrition, exercise and rest”, which are the basic concepts of “Health Promotion”, have been created from a lot of scientific evidence; but it might simply be a pattern of necessary daily behavior in animals. Namely, animals must perform severe exercise, for example “hunting”, to supply the energy (nutrition) necessary for life activities. After eating, they take a “rest” at a safe place in order to reduce consumption of energy acquired. The hunting behavior and the behavior of trying to escape from an enemy are radical exercises that induce damage to the skeletal muscle; and then these behaviors cause a temporary immune-suppression state. As well as animals, humans also have immune-suppression after strenuous exercise, that is called the “open window theory” (Fig. 1B, by Pedersen and Ullum2)). However, it is still unclear to scientists how they can understand its physiological significance.

It is known that toll-like receptors (TLRs) are an important recognition system when pathogens invade the body. TLRs are a kind of innate immune system, and 13 species have already been identified. Each TLR recognizes different pathogen-associated molecular patterns, respectively (elicits immune responses)3) (Fig. 2). We have reported that most TLR functions are suppressed by exhaustive exercise4). On the other hand, we showed that only the function of TLR5, which acts in intestinal immunity, occurred to a different response compared to other TLRs5). Here we propose the “super homeostasis theory”, which means that the immune response after exhaustive exercise might be a reasonable reaction for humans and animals.

Exercise-induced immune suppression

Open window theory. It has been known that severe exercise, such as high intensity and/or exhaustive exercise, causes temporary immunosuppression. This is “the open window theory” proposed by Professor Bente K. Pedersen (Denmark) in 19942), and this theory has been supported by much evidence as one of the greatest theories in the scientific field of exercise and immunology. The “J-curve model”, proposed by Professor David C. Nieman (USA) in 19946), is another famous theory of exercise and immunology, and suggests that the risk of upper respiratory tract infection (URTI) in those who have high-intensity exercise habits is higher than URTI in those who do not have exercise habits (Fig. 1A). Indeed, previous studies with human subjects have reported that several components of both the innate (e.g., natural killer cell activity and neutrophil oxidative burst activity) and adaptive (e.g., T and B cell function) immune system exhibit suppressed function after acute severe exercise7,8). Also, previous studies, with experimental animal models, have shown that severe exercise induced increases in herpes
and influenza infections, and that the same exercise also increased the rate of motility of those viruses\textsuperscript{10-13}. Within consideration of these reports, we have investigated the mechanism of acute exhaustive exercise-induced immunosuppression by focusing on TLR functions.

**TLR functions in the open window theory.** Lipopolysaccharide (LPS), constituting the outer cell membrane of gram-negative bacteria, is the main molecule of endotoxin, and has been well-known for strongly inducing an innate immune response. LPS binds the TLR4 expressed on the cell surface, mainly of immune cells (Fig. 1). After that, intra-nuclear translocation of nuclear factor-kappa B (NF-κB) is promoted via intracellular signal transduction, and then various gene expressions are induced. Through these pathways, cytokines, chemokines

![Fig. 1](image1.png)  
**Exercise intensity**

**Fig. 1** Two the greatest theories on the influence of exercise on immunity. J-curve (A): a model of the relationship between exercise and risk of upper respiratory tract infection (Nieman et al., 1994)\textsuperscript{6}, and open window theory (B): after a bout of intense exercise, the immune system is suppressed, making the exerciser more susceptible to infection (Pedersen and Ullum, 1994)\textsuperscript{2}.

![Fig. 2](image2.png)  
**Fig. 2** Sensing of bacteria and virus by pattern recognition receptors (PRRs). TLR: toll-like receptor, LPS: lipopolysaccharide, MyD88: myeloid differentiation protein 88, TRIF: Toll/IL-1domain containing adaptor inducing IFN-β, IRF: interferon regulatory factor, NF-xB: nuclear factor-xB, Nod: nucleotide-binding oligomerization domain, RIG: retinoid-inducible gene, ssRNA: single stranded RNA, dsRNA: double stranded RNA, TNF: tumor necrosis factor, IL: interleukin, and IFN: interferon. (Yano et al., 2012)\textsuperscript{4}
and other molecules are synthesized and secreted. However, it has been reported that this immune response is remarkably suppressed after exhaustive exercise. Kitamura et al. (2007)\(^ {14}\) showed that exhaustive exercise-induced immune suppression is greatly inhibited by specifically inhibiting the β-adrenergic receptor (Fig. 3). It has been pointed out that immunosuppressive factors by severe exercise are catecholamine, such as adrenaline and noradrenaline, and/or the adrenocortical hormone (glucocorticoid). At least, our experimental model suggests that the influence of catecholamine is larger than glucocorticoid.

In addition, although pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-α), production is induced when TLR3 (Fig. 1) recognizes double stranded RNA (dsRNA), this cytokine production is also suppressed by exhaustive exercise\(^ {15}\). Also, catecholamine, which is caused by exhaustive exercise, suppresses TNF-α production via TLR 7/8, which recognizes single stranded RNA (ssRNA). This phenomenon is demonstrated by experiments using the imidazoquinoline, R-848, which is a ligand of TLR 7/8\(^ {16}\). Therefore, these phenomena suggest that the open window theory may cover cases of virus infection via TLRs. Catecholamine binds to α- and β-adrenergic receptors on surface cell membranes. And then, this hormone/receptor complex activates adenylate cyclase via the G protein, resulting in ATP-derived cAMP phosphorylates protein kinase A turning into an active form. Although it has been known that this pathway inhibits both the NF-κB-dependent and -independent pathways, it had been unknown whether exercise suppresses either or both their pathways. Tanaka et al. (2010)\(^ {17}\) reported that TNF-α suppression, due to exhaustive exercise, has occurred without inhibition of TNF-α mRNA expression. Accordingly, it suggests that the mechanism, which is catecholamine-mediated inhibition of TNF-α production by exhaustive exercise, is an NF-κB-independent pathway. Namely, severe exercise-induced immune suppression might be regulated by a post-transcription process. This immunosuppression via TLRs does not occur at low and moderate intensity exercise\(^ {18}\).

Repeated excessive contraction of skeletal muscle, such as eccentric contraction, causes microscopic damage to the muscle fibers, and is considered to be structural destruction of muscle fibers caused by local mechanical stress. Then, along with the infiltration of leukocytes, active oxygen production, muscle protein degradation, cytokine and growth factor production, tissue repair occurs in a time series. It is also a fact that in this series of physiological processes, we experience aching pain such as delayed-onset muscle soreness (DOMS)\(^ {19}\). We have strongly thought that temporally immune suppression caused by severe exercise might be closely related to these physiological responses. Exercise-induced damage of muscle fibers is an important factor causing inflammation by invaded immune cells, neutrophils, macrophages and others. If after severe exercise, inhibition of inflammatory cytokine production, that is the open window, is not induced, it is easy to imagine that excessive inflammation will occur in various locations of the skeletal muscles. As for results, humans and animals will suffer from dangerous pain, fever and edema. However, animals are able to control the excessive inflammation in

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**Fig. 3**  Schematic depiction of the suppressive effect of exhaustive exercise on TNF-α production in the LPS signaling pathway. TNFR: TNF receptor, sTNFR: soluble TNFR, and mTNFR: membrane TNFR. (Yano et al., 2012)\(^ {16}\)
their muscles by catecholamine secretion, which means the activation of the central nervous system. We can say that it is a super homeostasis system for exercising animals. In addition, suppression of TNF-α production after exhaustive exercise was suppressed at the translation process, but not at the transcription level. Therefore, recovery from immune suppression is possible in a short time compared with suppression at the transcription level (that is exactly a temporally open window). In this way, it is thought that immune suppression recovers quickly and shifts to repair the muscle, which was damaged by strenuous exercise. In order to maintain life, the central nerve regulates the biological response, which appropriately suppresses severe inflammation of skeletal muscle, after exercise. As a result, it seems that the immune function after exercise is inevitably suppressed. This might be a very reasonable judgment as a biological response. Furthermore, by considering more deeply the immunosuppression phenomenon after this exercise, it is easy to understand the qualitative importance of a rest as the next stage after severe exercise. Namely, when we are thinking about conditioning for athletes, the resting method, which secures a cleaner environment after severe exercise (for example, games, competition and hard exercise training), is an indispensable resting behavior against the open window. For athletes, it is important not only how long to, but also where to take a rest. On the other hand, the compensatory effect is not completely lost to immunosuppression after severe exercise. It is known that phagocytosis of macrophages increases after acute exercise and anti-inflammatory type macrophages show high chemotaxis to damaged skeletal muscle.

**TLR5 functions during and after exhaustive exercise.**

In contrast, we have recently observed a very interesting phenomenon. That is a phenomenon in which immunosuppression after exhaustive exercise is avoided locally. Flagellin (FG), a flagella protein, is one of the pathogen-related molecules recognized by TLR5 (Fig. 1). Uchida et al. (2014) showed that TNF-α production via TLR5 in response to FG stimulation is different from the response of other TLRs. In other words, FG-induced TNF-α production was not suppressed by exhaustive exercise, but rather was accelerated (Fig. 4). Furthermore, our study pointed out that this response may not be caused by immune cells, such as macrophages, but by the mucosal epithelial cell line of the intestinal tract.

Finally, the finding that surprised us the most was that catecholamine-induced TNF-α production was enhanced via TLR5 in response to FG stimulation (Figs. 5). The
reason for this is that catecholamine, one of the major hormones induced by intense exercise\textsuperscript{14,22}, has been shown to suppress TNF-\(\alpha\) production in response to LPS/TLR4\textsuperscript{14,23}, poly I:C/TLR3\textsuperscript{15} and R-848/TLR7/8\textsuperscript{16} via \(\beta\)-adrenergic receptors. Accordingly, this is, to the best of our knowledge, the first study to demonstrate that TNF-\(\alpha\) production was accelerated in response to FG via TLR5 inducement, even when the mice were subjected to exhaustive exercise stress (Fig. 6). Godínez-Victoria et al. (2012)\textsuperscript{24} reported that strenuous exercise elicits higher levels of secretory IgA and polymeric Ig receptors in the small intestine in mice. In addition, another study showed that in a time-to-exhaustion trial (TTE), the rates of secretion of both salivary IgA and salivary lysozyme were increased in humans\textsuperscript{25}. Interestingly, the researchers suggested that these effects appear to be associated with changes in sympathetic activity, not the hypothalamic-pituitary-adrenal (HPA) axis. In intestinal lymphocytes, exhaustive exercise increases the TNF-\(\alpha\), IL-6 and IL-1\(\beta\) levels in mice\textsuperscript{26}. Therefore, the upregulation of the gastrointestinal immune response to severe exercise is important for self-defense systems, as well as the inhibition of the immune response in immune organs; opposite responses are regulated by sympathetic activity such as elevation of catecholamine secretion.

These facts overturning our original hypothesis came as a great surprise. On the other hand, the facts might give us the opportunity to rethink “What is health promotion?”

Anti-open window phenomenon in intestinal tract. In order to escape from starvation, animals that need nutrition from others must choose hunting behaviors such as exhaustive exercise. In contrast, the prey animal tries to escape from the predator (evade capture). Thus, in any case, an interlock of starvation, exercise and nutritional supplementation is a daily life pattern in wild animals. And exhaustive exercise, which is associated with local and systemic inflammation via repeated skeletal muscle contraction, might be the most required exercise style for animals. Accordingly, suppression of systemic inflammation after severe exercise is essential.

On the other hand, even if animals can eat their food after hunting, they must deal with another risk, which is bacteria and viral infection from the food consumed in the gastrointestinal tract during digestion and absorption. At this time, the immune function in the intestinal tract must be exerted just after severe exercise when the skeletal muscles have to avoid excessive inflammation. Therefore, it is a well-constructed system that the two different immune responses (immune suppression and activation) are induced at each local organ by the central control. Thus, after the energy supply is completed, the predator animals avoid unnecessary hunting until the next hunger phase, and keep on resting for conserving energy. This cycle of “exercise”, “nutrition” and “rest” might be the ideal lifestyle (basic health) for animals including humans. And also, as one of the biological mechanisms adapted to this cycle, the exercise-induced immune response system shown here might have been acquired in the evolution process (Fig. 7).

Conclusion
In this review, the physiological or biological significance of the “open window theory”, in which exercise advocated by Professor Bente K. Pedersen suppresses immunity, might have been found in part as a magical hypothesis “super homeostasis theory”. From the perspective of central control, it is surprising that this novel biological function organizes its biological defense during a period of severe exercise; it seems that our understanding of health and immunity has advanced to where we can begin to understand and appreciate such unique biological wonders.
Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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