

The Neuromuscular Junction: Structure, Function, and its Role in the Excitation of Muscle

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ABSTRACT

The neuromuscular junction plays a vital role in the function of skeletal muscle. It is responsible for transducing the excitatory electrical impulse from the nervous system to the muscle fiber, resulting in a muscle fiber action. The neuromuscular junction has also been implicated as a possible site of fatigue leading to muscle failure, and consequently to diminished athletic performance. Research has indicated that the structure and function of the neuromuscular junction adapts to exercise training. However, further research is needed to fully elucidate these adaptive responses and their impact on athletic performance. This brief review discusses the structure and function of the neuromuscular junction, the essential part that it has in the excitation/contraction process of skeletal muscle, and its adaptability to exercise training.

Key Words: synapse, motor endplate, acetylcholine, nerve terminal, fatigue

Introduction

The neuromuscular junction (NMJ) has been the subject of numerous investigations since the turn of the century. Early on, the NMJ served as a model for the study of synaptic transmission because of its ease of accessibility compared to other synaptic junctions. In fact much of the initial data used to elucidate and explain synaptic transmission emanated from work with the neuromuscular junction (22, 30, 35).

Over the years, neurobiologists' ability to perform research on the NMJ has greatly improved due to technological and methodological advances. These include improvements in the field of microscopy such as the development and increased availability of the electron microscope and the laser scanning microscope.

Equally important has been the development of new methods of staining different features of the NMJ so that they can be more effectively visualized. For example, toxins such as conotoxin and bungarotoxin bind with high sensitivity and specificity to Ca⁺⁺ channels and acetylcholine receptors, respectively. These toxins can be conjugated to fluorescent dyes that enable scientists to easily visualize these features of the NMJ.

In addition, neurobiologists now use the growing knowledge of immunology to assist in their study of NMJ morphology. Antibodies that react with specific antigens of the motor endplate can also be conjugated to fluorescent dyes. Immunohistological techniques are regularly employed to visualize various components of the NMJ. Advances in the equipment and methods of electrophysiology have greatly contributed to the investigation of neuromuscular physiology. This information can be used by neurobiologists to enhance their understanding of synaptic structure and function throughout the nervous system.

Indeed, the NMJ continues to be regularly used to investigate the mechanisms by which electrical impulses generated by one excitable cell are propagated across the synapse to stimulate another excitable cell (23, 28).

Today, however, the NMJ is studied for reasons other than its accessibility. Currently the NMJ is studied to provide insight into the causes and etiology of some neuromuscular diseases and a greater understanding of the biochemical and functional plasticity of synaptic junctions (33, 36, 41). Particularly interesting to professionals who are interested in the study of muscle physiology is the role of the NMJ in eliciting muscular contractions.

Although the effects of exercise on the morphological (43, 44), biochemical (19, 25), and metabolic (18, 24) characteristics of skeletal muscle have been thoroughly investigated, data concerning the impact of exercise on the structure and physiology of the NMJ are sparse. This is unfortunate, since the importance of the NMJ in the excitation and consequent contraction of skeletal muscle is well established. The physiological and structural characteristics of the NMJ, its role in the excitation/contraction process, and its adaptations to exercise will be discussed in this brief review.

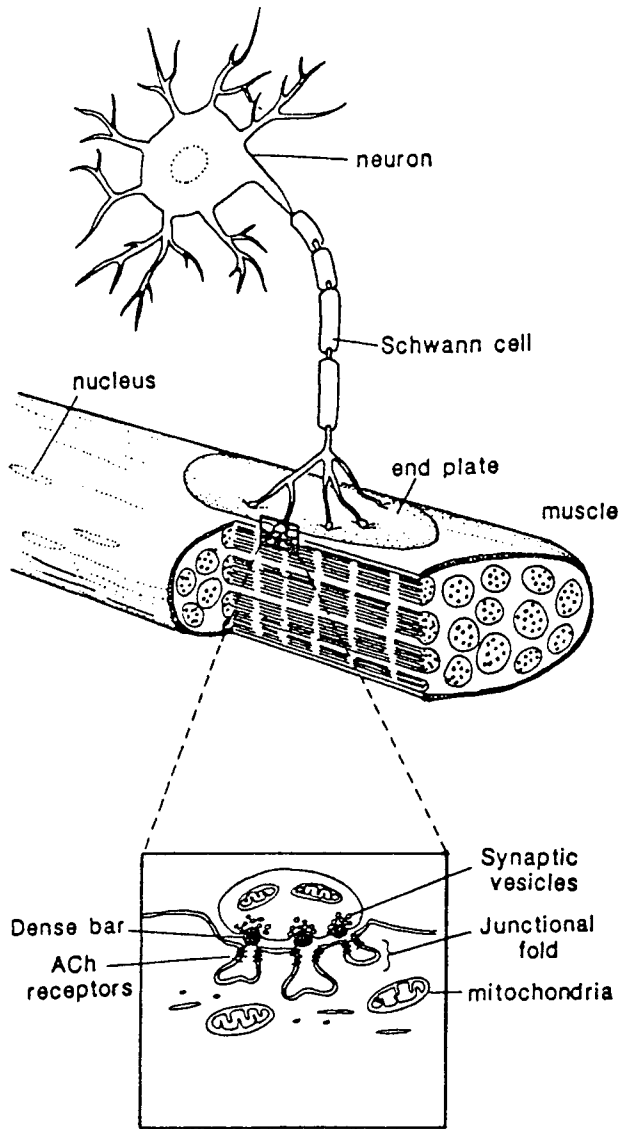


Figure 1. Illustration of the mammalian neuromuscular junction.

The Mature Mammalian Neuromuscular Junction

Structural Characteristics

Figure 1 presents a schematic of the structure of the NMJ. Although there appear to be numerous unique structural qualities of the NMJ depending on factors such as age, muscle fiber type, and degree of activity, all NMJs have five common features: (a) a Schwann cell that forms a cap above the segment of the nerve terminal that faces away from the postsynaptic region; (b) a nerve terminal that contains the neurotransmitter acetylcholine (ACh); (c) a synaptic space lined with basement membrane; (d) a postsynaptic membrane that contains ACh receptors; and (e) a junctional sarcoplasm and cytoskeleton that provides metabolic and structural support for the postsynaptic region (15).

The presynaptic region of the NMJ contains an unmyelinated axonal segment of the motor neuron

which then branches out into a series of nerve endings (10, 34). Typically these nerve endings form round or elliptical loops on the surface of the muscle fiber, and the size of these loops appears to be related to the size or diameter of the muscle fiber (22). These nerve endings appear as a thin filamentous network overlaying the surface of the muscle fiber.

Within the nerve terminals are several subcellular components including mitochondria, endoplasmic reticulum, lysosomes, and glycogen molecules. However, the most outstanding feature of the presynaptic nerve terminal is the abundance of storage vesicles containing Ach. Studies have indicated that there are approximately 50 to 70 Ach containing vesicles per μm^2 of nerve terminal area (9). The diameter of these vesicles varies from 30 to 50 nm (17). Along with Ach, these vesicles contain ATP and a proteoglycan (1). The vesicles are not randomly distributed throughout the nerve terminal, rather they appear concentrated along a thickened area of the nerve terminal membrane called dense bars. The term active zone describes the areas along the presynaptic membrane featuring dense bars and their associated rows of Ach vesicles (8).

Between the pre- and postsynaptic membranes is a narrow gap about 50 nm wide (21) that is referred to as the synaptic cleft. Recent data indicate that the pre- and postsynaptic components of the NMJ are not completely detached from each other. Balice-Gordon and Lichtman (6) have provided compelling evidence that the pre- and postsynaptic regions of the motor endplate are mechanically connected, if only indirectly, via the intervening basal lamina. This adhesion of the nerve terminal with the muscle fiber probably accounts for the tight coupling of the pre- and postsynaptic elements observed in the NMJ.

The postsynaptic membrane is a specialized region of the sarcolemma that contains depressions called synaptic gutters. Upon closer inspection these synaptic gutters are seen to contain finger-like protrusions of the membrane, called junctional folds, which extend toward the nerve terminals infiltrating the gutters. Along the crest of the functional folds are clusters of Ach receptors (3, 32). These junctional folds are in direct juxtaposition with the presynaptic active zones. Consequently, this arrangement allows the presynaptic Ach vesicles to be in direct apposition with the postsynaptic Ach receptors across the synaptic cleft.

The highly structured symmetry between presynaptic Ach vesicles and postsynaptic Ach receptors is depicted in Figure 2. The junctional folds are unique in that they are not found in the postsynaptic membrane of any other synapse of the nervous system. High concentrations of the enzyme acetylcholinesterase, which hydrolyzes Ach, are found at the base of these junctional folds. Also found near the base of the junctional folds are a large number of the mitochondria and nuclei of the muscle fiber.

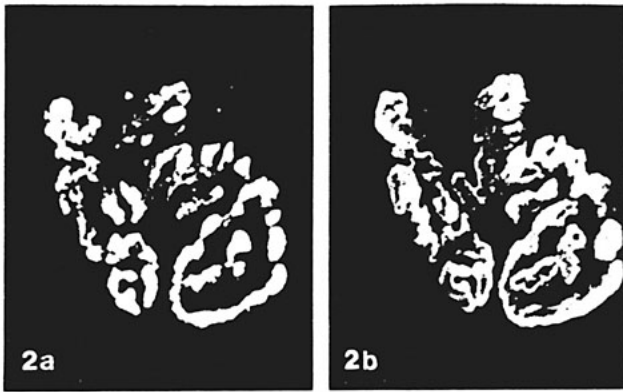


Figure 2. (a) Micrograph of the presynaptic face of the neuromuscular junction. The nerve terminal was stained with SV-2, an antibody that recognizes acetylcholine vesicles. Magnified 630 \times . (b) Micrograph of the postsynaptic face of the neuromuscular junction. The muscle fibers were stained with α -bungarotoxin, a snake toxin that recognizes acetylcholine vesicles. Magnified 630 \times . Note the almost perfect symmetry between acetylcholine vesicles and receptors.

Physiological Characteristics

The primary function of the NMJ is to transduce the electrical impulse, which propagates down the motor neuron from the higher neural centers, or from sensory neurons either directly or via interneurons, to the muscle fiber in order to initiate a muscle action. The NMJ is an atypical synapse in that it transduces only excitatory, and no inhibitory, electrical impulses to its postsynaptic cell (the muscle fiber). Initially this excitatory impulse is transmitted across the synaptic cleft to the endplate region of the muscle fiber, and this depolarization is referred to as the endplate potential (EPP).

Under normal or rested conditions, the EPP is of sufficient strength to elicit an action potential which is then transmitted throughout the muscle fiber by way of the T-tubular system, resulting in a muscle fiber twitch. However, during extended periods of activation the intensity of the EPP declines (14), and it may or may not be capable of eliciting an action potential, and thus a muscle action.

A very specific sequence of events occurs at the NMJ that allows an electrical impulse to be conducted from the motor neuron to the associated muscle fibers, resulting in a muscle contraction. As the electrical impulse, or action potential, propagates down the axon of the motor neuron, Ca^{++} channels distributed along the membrane of the nerve terminal are opened, resulting in an influx of Ca^{++} . The increased intracellular Ca^{++} concentration, via a mechanism that is still unclear, causes the release of Ach from the presynaptic terminal through an exocytotic event between the membranes of the Ach vesicles and the nerve terminal (21).

The latency period between the onset of the Ca^{++} current across the nerve terminal membrane and the release of Ach is extremely brief, indicating that the

Ca^{++} channels and the Ach vesicles are in close proximity with each other (17). Following the release of Ach from the nerve terminal, it appears that the membranous component of the vesicles is taken back up by the nerve terminal and repackaged with new Ach. The stores of Ach at the nerve terminal are replenished by the enzyme choline acetyl transferase, which uses Acetyl Co-A and choline as its substrates (40).

Following its release, Ach diffuses across the synaptic cleft and binds with the Ach receptors located on the crests of the junctional folds of the postsynaptic sarcolemma. This binding elicits an influx of Na^{+} across the sarcolemma at the endplate region, resulting in an electrical depolarization that is initially restricted to the endplate region of the sarcolemma. This EPP then evokes an action potential that is conducted throughout the entire sarcolemma via the T-tubular network which invaginates the muscle fiber. This transduction of the electrical impulse from the nerve terminal of the motor neuron to the endplate region of the sarcolemma, and then through the T-tubules, is considered to be the excitation phase of the excitation/contraction process.

The action potential of the T-tubules initiates the contraction phase of the excitation/contraction process. The actual event of the excitation/contraction process occurs at a specialized region where the membranes of the T-tubule and the intracellular sarcoplasmic reticulum are in close proximity. Here the T-tubular membrane is known to have a high density of dihydropyridine receptors which act as voltage sensors.

In apposition to these voltage sensors are ryanodine receptors, which are integral proteins of the membrane of the Ca^{++} rich sarcoplasmic reticulum. Called ryanodine receptors because of their affinity to the alkaloid ryanodine, these proteins are in fact Ca^{++} channels. It is postulated (37) that the mechanism involved in the excitation/contraction process begins with conformational changes of the voltage sensors of the T-tubule when it is excited, or depolarized, by an action potential.

The conformational changes of the dihydropyridine receptors then evoke conformational changes in the directly underlying ryanodine receptors located in the membrane of the sarcoplasmic reticulum. Once this occurs, these Ca^{++} channels are opened and Ca^{++} is released from the sarcoplasmic reticulum, resulting in an increased intracellular Ca^{++} concentration within the muscle fiber. Those Ca^{++} channels that are not contacted by dihydropyridine receptors are allosterically activated and opened when bound by the Ca^{++} released from the channels that are in contact with dihydropyridine receptors.

The release of Ca^{++} from the sarcoplasmic reticulum increases the cytosolic concentration of Ca^{++} about tenfold. This event triggers muscle contraction via the reaction of Ca^{++} with the troponin and tropomyosin complex. The troponin molecule is composed of three subunits. Troponin C contains both high and low affinity binding sites for Ca^{++} . Troponin I binds to actin,

which along with myosin acts as the contractile filaments within the muscle fiber. Finally, troponin T binds to the tropomyosin molecule which is interwoven with the actin molecule.

When the muscle fiber is in a relaxed state, this arrangement allows tropomyosin to mask the active sites on the actin filament. Also, when the muscle fiber is in its resting state, only the high affinity binding sites of troponin C are occupied by Ca^{++} . But when the sarcoplasmic reticulum releases Ca^{++} , the low affinity binding sites of troponin C also become occupied by Ca^{++} . This results in a conformational shift in troponin C, and thus the entire troponin molecule. In turn, there is an alteration in the position of tropomyosin, which unmask the active sites of actin and allows actin/myosin cross-bridge formation (47). The resulting muscle twitch completes the excitation/contraction process. The sequence of events involved in the excitation/contraction process is shown in Figure 3.

The excitation of the postsynaptic membrane is terminated when the ionic channel that is an integral component of the Ach receptor converts to a closed state; this conversion is governed by a predetermined

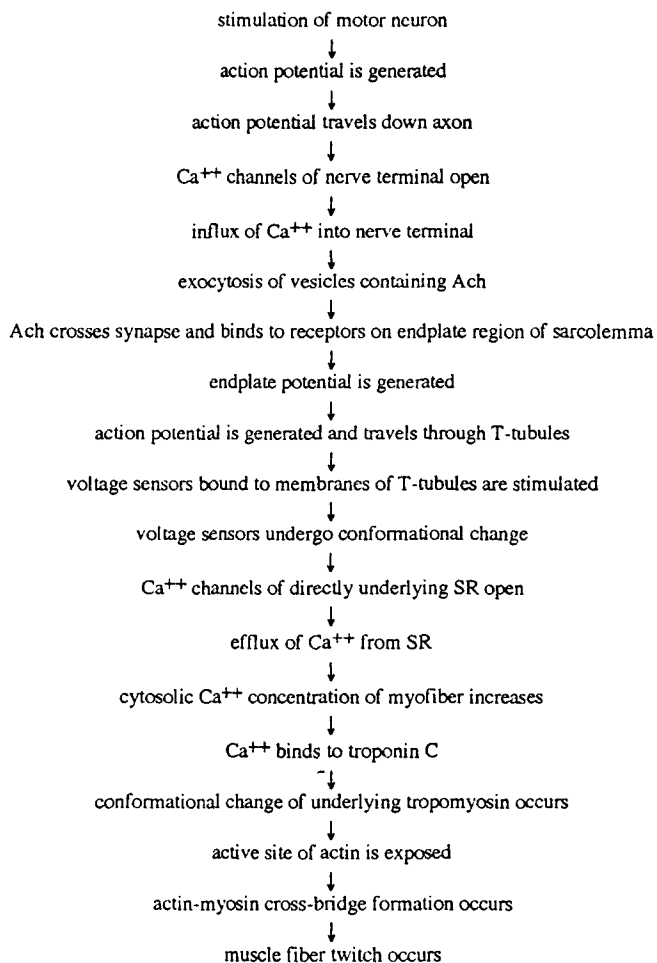


Figure 3. Sequence of events comprising the excitation/contraction process. Ach = acetylcholine; SR = sarcoplasmic reticulum.

rate constant (2). Subsequent to this, Ach dissociates from the Ach receptor and the neurotransmitter diffuses into the synaptic cleft. Acetylcholinesterase, located at the base of the junctional folds, then acts to hydrolyze Ach. The resulting choline is then available for re-uptake by the nerve terminal and utilized as a substrate for the synthesis of more Ach (40). However, it has recently been suggested that specific isoforms of acetylcholinesterase may be directly responsible for the termination of the endplate potential by hydrolyzing the Ach while it is still bound to its postsynaptic receptors (26).

Significance of the NMJ to Exercise Scientists

As stated, the effects of exercise training on muscle tissue have long been the subject of scientific investigation. By comparison, little data are available on the adaptations of the NMJ to exercise training. The focus of most early studies involving the effects of exercise and the NMJ was the prophylactic effect that exercise may have on the degenerative effects of aging. For example, it is known that aging is associated with a progressive atrophy of muscle fibers, termed senile muscular atrophy (16). It has been suggested that the degeneration of the NMJ seen in aged animals precipitates senile muscular atrophy (20). In addition to the morphological changes seen in aged NMJs is a diminution in their ability to sustain synaptic transmission (42), which in turn is associated with a decrement in muscle performance.

In their investigation on the relationship between activity and the NMJ in older animals, Stebbins et al. (45) concluded that exercise elevates the functional demand on the neuromuscular system, resulting in significant increases in nerve terminal sprouting and, consequently, in the area of neuromuscular contact. In a similar study, Rosenheimer (38) demonstrated that endurance training offsets the reduction in nerve terminal area typically observed in aged mammals. That study documented an increased incidence of nerve terminal sprouting in both the fast-twitch EDL muscle and the slow-twitch soleus.

In contrast to that study, Andonian and Fahim (4) found that aging resulted in more complex nerve terminals featuring increased branching areas. However, similar to the findings of Rosenheimer, they demonstrated that exercise training can ameliorate the age related changes in NMJ morphology. In both middle-aged and senescent animals, exercise effectively prevented the expansion of the nerve terminal seen in untrained, age-matched controls. The results of both studies clearly indicate that exercise training mitigates the neuromuscular degeneration observed in the aging process.

More recently, the effects of exercise training on the motor endplates of young, healthy animals have

been investigated. Waerhaug et al. (48) demonstrated that endurance training amplifies nerve terminal areas in the soleus muscle. However, it should be noted that training resulted in a similar increase in the diameter of the muscle fibers of the soleus. Since it has been found that NMJ area increases in parallel with the normal growth of muscle associated with the natural development of untrained animals (6, 31), it may be that the enlargement of NMJs found by those investigators is merely due to training induced muscle hypertrophy of the soleus. That same study reported different results in the EDL muscle. While no training-elicited expansion of the nerve terminal occurred in this fast-twitch muscle, exercise reduced the diameter of the EDL's fibers. Consequently, the ratio of nerve terminal area to muscle fiber size was significantly elevated in exercise trained animals compared to untrained controls.

Another study has demonstrated that the NMJs of slow- and fast-twitch muscle respond differently to endurance training (5). While endurance training effectively increased nerve terminal areas in both the soleus and EDL muscles, the degree of those changes was greater in the fast-twitch EDL. And although endurance training did not alter the number of nerve terminal branches in the soleus, branch number in the EDLs of trained animals was found to be significantly greater compared to untrained controls.

The results of Deschenes et al. (13) indicate that the adaptations of the NMJ to exercise training are dependent upon intensity. These investigators used techniques that visualized Ach vesicles, Ach receptors, and neurofilaments. Thus, synaptic contact points as well as nerve terminal branching patterns were able to be quantitated. It was determined that high intensity training elicited more complex nerve terminal branching patterns than low intensity training. In addition, although both high and low intensity exercise training brought about expanded NMJ areas, the former resulted in more dispersed synapses while low intensity training resulted in more compact motor endplates. Significantly, the exercise related NMJ expansion documented in this study was not associated with muscle fiber hypertrophy. This suggests that exercise stimuli increase the area of the NMJ directly, rather than indirectly as a result of muscle hypertrophy.

Endurance exercise has also been found to alter the physiological characteristics of the NMJ. Dorlochter et al. (14) reported that EPP amplitudes were greater in endurance trained animals compared to untrained controls. This suggested that, upon stimulation, the nerve terminals of trained animals released greater amounts of neurotransmitter than the nerve terminals of the controls. Clearly, NMJs, like muscle fibers, undergo adaptive responses to endurance training that are probably designed to delay the onset of fatigue. The biochemical causes of fatigue within the muscle fiber itself have been previously reviewed (12).

Unfortunately, there is little information on the effects of resistance training on the NMJ. It is known that motor unit recruitment patterns and firing rates of the nervous system determine the force developed by a muscle (11). At least one study implicates the NMJ as a potential site of fatigue. Stephens and Taylor (46) demonstrated that during a maximal muscle contraction, the initial phase of muscle failure is brought on by fatigue of the NMJ.

While several studies have used electromyography (EMG) to investigate the effects of weight training on neuromuscular physiology (39), to our knowledge no invasive or in situ studies have been conducted to directly determine the effects of strength training on isolated, individual motor endplates. Further, data concerning the morphological adaptations of the NMJ to strength training are lacking. Most of these more direct, invasive techniques require the use of animals, and perhaps no completely satisfactory animal strength training model has been developed.

Previous research has demonstrated that the muscle hypertrophy observed during the normal growth and development of mammals is associated with expansion of the NMJ (6, 31). This suggests that exercise induced muscle hypertrophy may also be accompanied by hypertrophy of the NMJ.

Banks et al. (7) investigated the effect of compensatory muscle hypertrophy on motor endplate structure. In that study muscle hypertrophy was elicited via the surgical removal of the functional synergists. This resulted in an increased muscle fiber diameter of approximately 100%. Yet the area of the NMJs of these muscles was only 10 to 30% greater than those measured in controls who did not undergo surgery. Unfortunately, it is impossible to relate these findings with changes in NMJ morphology that might occur as a result of a formal weight training program.

Exercise scientists have demonstrated a process of "disinhibition" which can occur following participation in a well-structured weight training program (29). It is believed that this exercise induced disinhibition is a physiological adaptation of the nervous system that decreases the amount of inhibitory neural input delivered to contracting skeletal muscles. Consequently, there would be an increase in the intensity of the excitatory stimulus delivered to the muscle, leading to an increase in the force produced by the muscle contraction.

However, the focus of this adaptation is not the NMJ. The nerve terminals of the motor neurons that innervate skeletal muscle do not contain or release inhibitory neurotransmitters (15). In contrast, the cell bodies of the motor neurons, which reside in the spinal cord, do commonly receive both excitatory and inhibitory stimuli from other neurons of the central nervous system (27).

Disinhibition is either the result of a decreased sensitivity of the cell body of the motor neuron to

inhibitory neurotransmitters, a reduction in the amount of these inhibitory neurotransmitters delivered to the motor neuron at the spinal cord, or a combination of the two. Thus, while disinhibition affects the motor neurons that innervate skeletal muscle, it is an adaptation of the central (i.e., the spinal cord) and not the peripheral (i.e., the NMJ) nervous system.

In summary, those interested in properly training athletes to achieve optimal performance must not overlook the importance of the neuromuscular junction. This structure plays an essential role in the excitation/contraction process of muscle. Research has demonstrated that endurance training elicits morphological and physiological adaptations of the NMJ. Unfortunately, the effects of structured weight training programs on the NMJ remain unknown. Future studies revealing the functional and structural adaptations of the NMJ to strength training are imperative if we are to fully appreciate the physiological mechanisms involved in athletic training and conditioning.

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Acknowledgment

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