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When an octopus has MS: Application of neurophysiology and immunology of octopuses for multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an immune-mediated disease which can cause different symptoms due to the involvement of different regions of the central nervous system (CNS). Although this disease is characterized by the demyelination process, the most important feature of the disease is its degenerative nature. This nature is clinically manifested as progressive symptoms, especially in patients' walking, which can even lead to complete debilitation. Therefore, finding a treatment to prevent the degenerative processes is one of the most important goals in MS studies. To better understand the process and the effect of drugs, scientists use animal models which mostly consisting of mouse, rat, and monkey.

In evolutionary terms, octopuses belong to the invertebrates which have many substantial differences with vertebrates. One of these differences is related to the nervous system of these organisms, which is divided into central and peripheral parts. The difference lies in the fact that the main volume of this system expands in the limbs of these organisms instead of their brain. This offers a kind of freedom of action and processing strength in the octopus limbs. Also, the brain of these organisms follows a non-somatotopic model. Although the complex actions of this organism are stimulated by the brain, in contrast to the human brain, this activity is not related to a specific region of the brain; rather the entire brain area of the octopus is activated during a process. Indeed, the brain mapping or the topological perception of a particular action, such as moving the limbs, reflects itself in how that activity is distributed in the octopus brain neurons. Accordingly, various actions are known with varying degrees of activity of neurons in the brain of octopus. Another important feature of octopuses is their ability to regenerate defective tissues including the central and peripheral nervous system.

These characteristics raise the question of what features can an octopus show when it is used as an organism to create experimental autoimmune encephalomyelitis (EAE). Can the immune system damage of the octopus brain cause a regeneration process? Will the autonomy of the organs reduce the severity of the symptoms?

This article seeks to provide evidence to prove that use of octopuses as laboratory samples for generation of EAE may open up new approaches for researchers to better approach MS.

Introduction

Multiple sclerosis (MS) is a disease of the immune system which can lead to various symptoms through affecting the central nervous system (CNS). Different immune cells, including B cells and T cells, are involved in the development of this disease [1]. In terms of pathology, MS is characterized by a series of demyelinating plaques in the white matter of the brain [2].

Although it is now known that the grey matter of the brain is also involved in this disease, new imaging and pathology methods have shown that normal-appearing white matter is not normal in this condition, where numerous defects have been observed in more accurate imaging methods. All these contribute to the development of clinical symptoms [3–5]. Indeed, a new demyelinating plaque may be associated with clinical symptoms [6].

Although demyelination is a known aspect of MS, the main manifestation of the disease (i.e., progressive and neurodegenerative nature) is due to axonal injury, with evidence suggesting that axonal damage occurs from the very beginning of the disease [7].

Axonal damage is characterized clinically by progressive phase. With the natural course of the disease, most patients with relapsing-remitting MS turn into a secondary progressive type in the long run [8,9].

The primary progressive MS also affects 10–15% of patients with MS

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[10]. Clinically, this clinical progression is mostly manifested as a disturbance in walking. Further, the most common clinical sign in primary progressive MS is spastic paraparesis [11].

In general and regardless of the disease phase, walking disorder is one of the most important complaints of patients. Specifically, 58% of patients complain about the different aspects of this disorder in the first year of their illness. Over the upcoming ten years, this will reach 93% [12]. Furthermore, 70% of MS patients consider walking disorder as the most important clinical problem of the disease [13].

The pathophysiology impact of MS which is a CNS disease has also been studied in the limb muscles affected by the disease. It has been shown that not only muscle strength and muscle mass are reduced, but also muscle fibers as well as the type I, II, and IIa muscle fibers shrink compared to normal people [14].

The muscular weakness (i.e., effects in the neuromascular system) is caused by lesions in the central nervous system. This is because in our bodies, peripheral organs such as peripheral nerves or muscles are under the control of the CNS. Therefore, any disease that affects the CNS has the potential to have an effect on the neuromuscular system and, as with MS, cause walking disorder.

So, it can be hypothesized that if the peripheral organs can be partially free from the CNS power and have a self-regulating property, the symptoms of CNS diseases will also diminish. This self-regulation and autonomy can take place in two ways. First, there should be areas with processing ability in the peripheral organs. Secondly, the CNS processing changes in a way as it allows self-regulation and autonomy of the limbs.

Possibly at the first glance, such an intention is out of reach, but in nature there are patterns that can help us achieve this. In this regard, octopuses are the key to solve this problem. These organisms have characteristics that can help us develop new strategies for treating MS.

The nervous system of the octopus versus the human nervous system

As Penfield has shown, the brain can be divided into several centers, the stimulation of which may stimulate a certain region of the body. These findings led to the development of the famous Penfield homunculus, according to which and depending on the sensory or motor function of the cortex, a plan is depicted as a homunculus with an abnormal shape [15]. The so-called brain division and mapping is referred to somatotopic arrangement. In this way, it is possible to determine various centers, with stimulating each of which the corresponding area of the body begins to move. The correspondence of a region in the brain to a part of the body is also applied regarding the sensory cortex [16,17]. Nevertheless, such a somatotopic arrangement and one-to-one correspondence is not seen in octopus vulgaris (octopus) [18,19]. We encounter a small brain in octopuses, surrounded by large peripheral nerves. Two-thirds of this CNS includes the optic lobes [20]. According to the experiments, there is no somatotopic set up in the brain. Although complicated actions are performed by the stimulation of the brain, unlike the human brain, this activity is not related to a specific region of the brain; rather, the entire brain area of the octopus is activated during a process. Indeed, the brain mapping, or topological perception, manifests itself by how the activity is distributed across the octopus brain. In other words, the stimulation of a neuron in the octopus brain does not cause a simple movement in one organ, but leads to a complex movement. The complexity of the so-called movement is different with regard to the intensity of the stimulation. The stimulation of higher motor centers in the octopus brain triggers the movement of several arms which is not limited, as in humans, to merely stimulating a single movement in one limb. Interestingly, representation in the brain and CNS of the octopus is more like a representation of a motion program, instead of representing a part of the octopus body. Therefore, the performance of the higher motor centers seems to be mainly focused on determining the program and type of movement. This means that you cannot see the somatotopic map or Penfield homunculus in the octopus brain. This non-restriction of functional areas in the brain in turn contributes to more freedom of the organs. It is very important and interesting to note that what has been said does not infer that the octopus arms are purely autonomous for a simple mobility. Instead, research has shown that, for example, for a complex movement such as eating and taking food into the mouth, octopuses use a human-like strategy, except that this strategy is planned within the arms [21,22].

On the other hand, each octopus arm has the ability to form a kind of peripheral planning, which also helps the free movement of each arm [23]. These pieces of evidence all suggest a self-organized embodiment in the nervous system of octopuses [24–26], which has been caused by the wide spread nervous system throughout the entire body of the octopus. Indeed, the bulk of the octopus neurons is located in its eight arms [27].

In other words, an octopus has nine brains rather than one. One brain is located in the central nervous system, and the other eight brains are located in its limbs. The CNS sends general instructions and delegates details of the tasks to the limbs. Therefore, the limbs have significant degree of autonomy [28]. Each limb has numerous suckers that act as the tactile sense in octopuses. They can recognize other limbs by these suckers through a chemical self-recognition system and thereby preventing intersection of the arms [29].

If there is a top-down hierarchy in the human nervous system for the functioning of a system, here, the entire focus is on the totality of the system, where an intelligent behavior stems from the interrelated and complex interaction of physical capabilities, information system, and peripheral environment. Such a system guarantees the best behavior in relation to the so-called ecology. At the same time, the system performance becomes easier and requires less energy.

In brief, the difference between the human and the octopus nervous system can be summarized as follows: absence of a somatotopic arrangement in the CNS and existence of a kind of self-regulation and autonomy as well as the ability to perform planning in the peripheral organs. Hence, the following question can be raised: If the CNS is damaged in an octopus, what effect will it have on the overall behavior of the animal?

We believe that as no definite cure has been found so far for MS, despite the growing research, searching through unconventional ways is worthwhile. So, we can take a step further and try to answer this question.

The immune system of octopuses

Octopuses, as other invertebrates, lack the adaptive immune system, which means that immunoglobulins or T-cell receptors that play a vital role in the development of MS cannot be found in octopuses [30]. However, innate immune system has a major role in the immunity of octopuses. The function of such an immune system is divided into cellular and humoral components [31].

Immune system response is mainly initiated by the cellular component, in which hemocytes and white body cells play a significant role [32]. In invertebrates, hemocytes play the same role as granulocytes in vertebrates and cause cytotoxicity, phagocytosis, and wound healing [33].

Apart from the cellular response which is the primary protective immune mechanism of the octopuses, the humoral component with its different roles triggers the immune responses. These roles include identifying and marking foreign substances, affecting the secretion of proteolytic enzymes, and creating a proto-complement system for better defense of octopuses against the bulk of pathogenic organisms [30,31].

Thus, the mechanism of the immune system in octopuses is fundamentally different from that of humans as both innate and adaptive immune systems are highly active in the human body.

What happens when an octopus has MS?

So far, no symptoms of MS-like disease have been observed in octopuses. Indeed, this is a new research work in which the octopuses are used as laboratory samples for generating experimental autoimmune encephalomyelitis (EAE) specimens. Note that it is only with laboratory work that one can answer these questions. EAE is increasingly used as laboratory samples for inflammatory diseases of the brain, especially MS. In these samples, pathological factors of MS disease, such as axonal injury, inflammation, and demyelination have been observed [34].

Animals mainly used to create EAE include monkeys [35], mice [36], and rats [37].

From the point of view of our discussion, their most important commonality with humans is that all these species are vertebrates. According to this and evolutionarily, the form and morphology of the nervous system development as well as the function of the system in these organisms are very similar to humans', and the same top-down domination of the CNS with respect to the peripheral nervous system can be observed. Clearly, these organisms have a deep phylogenic difference with octopuses, which is why octopuses have not been used so far to create the EAE model. However, according to what was stated earlier, it seems that examining EAE models that use octopus can afford us valuable information.

With this introduction, we will return to the headline of this section of the article: "What happens when an octopus has MS?". Evidently, this question cannot be asked at this time and we should wait for laboratory studies. Nevertheless, there are some points about the octopuses that could in part increase our hope for the possible findings from future studies. One of the most important challenges in MS is preventing axonal degeneration. Progressive damage of axons practically leads to patients' clinical disability. When myelin coating of axons is damaged, they are exposed to damage induced by immune system [38]. Therefore, one of the most important goals in dealing with MS is producing drugs that can cause myelin regeneration [39,40].

This is a very important and great goal in improving the condition of MS patients. However, the complexity of the work as well as numerous pathophysiological barriers still prevents it [41]. If studies can stimulate remyelination and generate it in damaged cells, it may be possible to prevent the progression of the disease to a large extent as well as its problems including walking disorders. Therefore, finding patterns that can create or accelerate this process is one of the most important research priorities in MS.

This is a very important point that is observed in octopuses. The octopuses have the ability to completely regenerate various organs including the central and peripheral nervous system, after they have been completely cut, whereby axons re-grow in this process. How octopuses can recover considerably and repair and re-grow their lost members has been the subject of numerous research studies [42–44].

Nevertheless, these studies have mainly focused on molecular and cellular regeneration mechanisms. Consideration of the role of hemocytes in the regeneration process has been one of the most important findings in this regard. In the aftermath of injury, we are faced with a kind of lesion and reproduction of hemocytes [45]. Hemocytes produce factors that contribute to the growth of axons. In general, research has reported their major role in the regeneration process of octopuses [44]. However, there are still many questions about this potential [46].

The major drawback of this research is that it has not been clinically taken into account. If we look at MS clinically, for example, with regard to the possibility of using research studies in the treatment of MS, new questions will arise that can even help zoologists in their investigations. These studies all speak of cutting the nerve, while the process occurring in MS is not cutting the nerve. In this condition, the patient experiences myelin as well as axonal damage. There is no cutting of the nerve, but the nerve is damaged. When the damaged nerve works badly, will the same regeneration process occur to heal it as in a cut nerve?

Perhaps CNS diseases in octopuses can answer to this question. Although infectious, skin, and digestive diseases have been reported in octopuses [47–50], none have indicated a disease that, like MS, causes involvement of the CNS of octopuses.

It is therefore very clear that artificial laboratory samples should be created in order to provide an appropriate answer to these questions. The questions are not limited to the type and location of the damage. Indeed, the following questions may be more important: Does the specific morphology of the octopus nervous system play a role in the regeneration of nerves after being cut? Can the regeneration of the nervous system after cutting a nerve be induced, to some extent, from the self-organized embodiment model? If a part of the octopus CNS is damaged, what effect does it have on the whole system? When a nerve is damaged due to MS, does its repair method also follow the same repair mechanism of the cut nerve? To what extent and how the self-organized embodiment is rehabilitated when the CNS of octopuses is damaged?

When we talk about the autonomy of the arms in octopuses, it immediately comes to the mind that if the CNS is disturbed by a disease such as MS, this autonomy reduces the damage to the arms and prevents their loss of ability. This is exactly the opposite of what is seen with the attack or progression of the disease in MS. The question is: "Does this really happen?" As mentioned above, these are very important questions that should be answered in the laboratory. That final question is: "Can creation of EAE laboratory samples with octopus instead of rats or monkeys bring about a major development in the laboratory investigation of MS?"

How can the points above help us in treating MS?

In the previous sections, it was stated that octopuses lack an adaptive immune system. The mentioned point can greatly diminish the role of octopuses in better comprehension of MS. However, the innate immune system also plays a vital role in the development of MS. Given the unique features of octopuses, especially in healing wounds and injuries, a better understanding of the function of the innate immune system in octopuses can expand our knowledge about MS.

Possibly, this question would be answered by laboratory samples. If we can test MS in different patterns of the nervous system, then different strategies may emerge. It can also indicate to what extent the different nervous system of octopuses can be helpful in proposing new approaches to deal with MS. Apart from creating EAE samples with the help of octopuses, there are other important questions that should be answered in this research field:

Another critical point is a better understanding of the autonomy of limbs in octopuses and application of the autonomous mechanism in further improvement and efficiency of majority of the impaired organs in MS patients. Yet, given the role of the CNS and its dominance in humans, it seems impossible to induce the mentioned autonomy in human organs. However, ganglions, which are masses of neurons located in the peripheral nervous system, can be considered for development of a degree of autonomy in the limbs impaired by MS. Particularly, it has been recently recognized that ganglions do not merely act as a means of transmitting information to the CNS; however, they can also partly interpret the information [51]. Moreover, they can exchange information among themselves through a GABA-dependent system [51]. Ganglions seem to be somewhat autonomous. Although this autonomy is still negligible and unidentified, it can be considered a potential candidate for this purpose.

If the self-organized embodiment model reduces the clinical symptoms in an octopus EAE model, can we help the human brain create some degree of such an organization via some kind of induced neuroplasticity?

A significant issue in the application of neurophysiology and immunology in octopuses to better understand MS is neuroplasticity which offers more effective therapies in this regard.

Neuroplasticity denotes any changes in the structure and function of the human brain in response to the individual's experiences [52]. Neuroplasticity involves several mechanisms and continually contributes to increasing the individual's brain capacity throughout his life. In general, neuroplasticity occurs under two distinct conditions: 1) during the normal development of the brain, a specific example of which is learning and the mechanism of memory and 2) during an adaptive mechanism for eliminating or reducing the brain injuries [53].

Although numerous studies have been conducted on neuroplasticity in humans and other vertebrates, few studies are devoted to address the issue of neuroplasticity in octopuses.

However, considering the immune system characteristics of these creatures, the unique function of their nervous system, and their tissue repair ability, we highlighted the necessity of adopting new perspectives in neuroplasticity in octopuses.

These are merely a part of the therapeutic approaches that this new treatment may provide. The author believes that the complexity of MS disease and the problems it creates for patients make it worthwhile to work on such a model.

Conclusion

The nervous system of octopuses is evolutionally different from humans'. This different nervous system affords octopuses some unique abilities and privileges which our bodies lack. The most important ability is the absence of somatotopic organization in the CNS and autonomy of the arms. Along with these features, it has been shown that due to molecular and cellular properties, these animals have the ability to repair their damaged members including the central and peripheral nerves. Since one of the most important problems of MS is the progressive degeneration, it seems that employing octopuses to generate EAE specimens may provide new insights into MS treatment.

Declaration of Competing Interest

The author declares that there is no conflict of interest.

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