

# Action Mechanism and Side Effects of Tetrodotoxin

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**Abstract.** Tetrodotoxin (TTX) is one of the most toxic neuro-toxins found in the world at present. This drug has been widely used in the medical field, such as treating cancer related pain and severe arrhythmias. It is widely distributed and has been found in various high and low organisms such as aquatic and terrestrial organisms. But the source of the TTX and detoxification methods still need to be studied, so the study of the TTX is very significant. At the same time, TTX can block sodium ion channels, has obvious analgesic effect, and also has antiarrhythmia, abandon drug addiction and other effects. As a result, TTX has high medical and commercial value. This research will mainly summarize the pharmacological action, side effects of TTX and its underlying principle. In addition, it is expected that this study can provide new ideas for the study of new functions of TTX and the treatment of new diseases.

**Keywords:** Tetrodotoxin, Action mechanism, Side effects.

## 1. Introduction

Tetrodotoxin (TTX) is a highly toxic non-protein toxin, the molecular formula is  $C_{11}H_{17}N_3O_8$ . It is slightly soluble in water, insoluble in organic solution and easy to decompose under alkaline conditions. It was first discovered in 1909 by Japanese scholar Ryojun Tahara from the puffer fish, and subsequently isolated in 1950 by Akira Yokao, Fujisuke Tsuda and others from the puffer ovary in the form of crystalline TTX. Different species contain toxins in different locations, but they are mainly distributed in the ovaries and internal organs. Because tetrodotoxin is highly toxic and unnoticed, the possibility of mistakenly ingesting tetrodotoxin is greatly increased, and it can be used by terrorists. The current detection technology includes bioassay, high performance capillary electrophoresis (HPCE), high performance liquid chromatography fluorescence detection (HPLCFLD) and enzyme-linked immunoassay (ELISA). Among them, ELISA is the detection method in the kit that can be bought on the market, and it is also the easiest way for people to test the toxins to get the results.

TTX is widely distributed in various species, so the origin of tetrodotoxin has become a hot topic to scholars. At present, there are four hypotheses about the origin of tetrodotoxin, which are endogenous theory, exogenous theory, food chain hypothesis and microbial origin hypothesis [1]. Endogenous theorists believe that puffer fish have specific functions or microorganisms that can convert ingested food into toxins. Exogenous theory was developed by Japanese scholars through feeding non-toxic puffer fish with TTX and eventually poisoning. The food chain hypothesis was put forward by foreign scholars who found that the toxins in the body of a conch were accumulated by eating starfish containing TTX. Ken Yasumoto, a Japanese scientist, found TTX in the pseudo-monas genus isolated from the guts of calcaria and poison crab, and thus proposed the hypothesis of microbial origin. At present, many microorganisms that can produce TTX have been found, so more and more scholars advocate the hypothesis of microbial origin.

Because of the unique structure and function of TTX, it is of great significance in pharmacological research and mainly used in anesthesia, prevention of renal failure, analgesia, drug withdrawal, anti-arrhythmia and so on [2]. At the same time, TTX, as a highly toxic natural toxin, is about 1,250 times more toxic than the highly toxic substance sodium cyanide and only 0.5 mg can kill a person. By combining with sodium ion channels, it blocks nerve conduction, and eventually leads to muscle and nerve paralysis and death, clinical reactions include nausea, vomiting, numbness of the lips and limbs, breathing difficulties, and finally shows paralysis of the whole-body muscle. The fish's delicious

meat attracts many people to taste, but the tetrodotoxin in it causes thousands of deaths every year due to improper processing. Therefore, in order to protect people's lives, it is very important to study the antidotes of TTX further by understanding the toxic principle and structural action of TTX. In this research, the mechanism, structure, side effects and pharmacology of TTX were reviewed to provide reference for further study of TTX antidotes.

## 2. Distribution and source of TTX

### 2.1. The distribution

TTX is a neurotoxin widely distributed in nature. Although it was originally isolated in puffer fish, it was later found to exist in a variety of different species as research continued. Tetrodotoxin is found in a wide variety of organisms, including some species of conch, worms, frogs, octopuses, and more.

For example, tetrodotoxin has also been reported to be present in some species of sea snails in the Indian and Pacific Oceans, possibly because these snails ate foods with tetrodotoxin [3]. In addition, some species of blue-ringed octopus also contain tetrodotoxin because they eat tetrodotoxin containing organisms. Other studies indicate that some species of poison dart frogs also contain tetrodotoxin, although the concentration of this toxin is much lower than in puffer fish. In addition, tetrodotoxin is also found in certain microorganisms, such as some bacteria and algae. This suggests that tetrodotoxin may be transmitted through the food chain.

### 2.2. Origin hypothesis

The source of tetrodotoxin has long been a point of debating. At present, there are four main hypotheses [4], which are endogenous theory, exogenous theory, food chain and microbial origin hypothesis.

**Endogenous theory:** The hypothesis is that puffer fish have specific functions or microbes that can convert the food they eat into toxins. This means that the puffer fish itself can produce tetrodotoxin.

**Exogenous theory:** This hypothesis was derived by Japanese scholars by feeding non-toxic puffer fish with bait containing TTX, and eventually poisoning occurred. This means that puffer fish cannot produce tetrodotoxin on their own, but rather ingest from the environment.

**Food chain hypothesis:** This hypothesis was proposed by foreign scholars who found that the toxins in a conch were accumulated by eating starfish containing TTX. This means that tetrodotoxin is spread through the food chain.

**Microbial origin hypothesis:** This hypothesis was developed by Ken Yasumoto from the discovery of TTX in the *Pseudomonas* genus isolated from the guts of lime algae and poison crabs, which implies that tetrodotoxin may be produced by certain microorganisms.

At present, the microbial origin hypothesis is widely accepted because a variety of tetrodotoxin producing microorganisms have been found and these microorganisms are present in a variety of organisms containing tetrodotoxin. There may be some truth to all four hypotheses, and the sources of tetrodotoxin may be various, possibly due to the physiological characteristics of the puffer fish itself, or its food chain, or the microorganisms that live in the puffer fish. TTX is widely distributed and presents in a variety of different organisms, and its sources may be many aspects, including the puffer fish itself, the food chain, and microorganisms. Further research is required to identify the specific sources of tetrodotoxin, which is critical to understanding the biological role of tetrodotoxin and developing new antidotes and drugs.

## 3. Toxic action mechanism of TTX

TTX is a highly toxic alkaloid with the molecular formula  $C_{11}H_{17}N_3O_8$ . Its molecular structure consists of a piperidine ring, a furan ring, and an alkyl side chain containing multiple hydroxyl groups, a carboxyl group, and a nitrogen atom [5]. This complex structure makes tetrodotoxin very biologically active. The molecular structure of tetrodotoxin allows it to bind to sodium ion channels

in the organism, thereby blocking the entry of sodium ions, which in turn affects the transmission of nerve signals.

The main mechanism of toxic action of TTX is to inhibit the transmission of nerve impulses by blocking sodium ion channels on nerve membranes. In normal circumstances, the transmission of nerve impulses is dependent on sodium and potassium ion channels in nerve cell membranes. When a nerve cell is stimulated, sodium channels in the membrane will open, allowing sodium ions to enter the cell from outside the cell, resulting in depolarization of the membrane, resulting in full nerve impulses transmission. Then, potassium channels open, allowing potassium to flow out of the cell, leading to repolarization of the membrane and completion of nerve impulse transmission. TTX binds to specific parts of the sodium channel so that the channel cannot be opened [6]. In this way, when the nerve cell is stimulated, sodium ions cannot enter the cell, the membrane cannot be depolarized, and nerve impulses cannot be generated. This mechanism of action makes TTX extremely toxic. Even a very small dose can quickly block the transmission of nerve impulses, leading to paralysis and death.

## **4. Pharmacological effects of TTX**

### **4.1. Clinical manifestations**

The clinical manifestations of TTX poisoning usually include the following aspects:

**Digestive symptoms:** TTX poisoning usually begins with digestive symptoms, including nausea, vomiting, abdominal pain, and diarrhea.

**Neurological symptoms:** Subsequently, the patient will experience neurological symptoms, including dizziness, headache, numbness of the mouth and lips, weakness of the limbs, muscle twitching, paralysis, and difficulty breathing.

**Cardiovascular system symptoms:** TTX can also affect the cardiovascular system, showing tachycardia, arrhythmia, hypotension and shock.

TTX poisoning is an acute form of poisoning in which clinical manifestations progress rapidly and symptoms may appear within minutes to hours of ingestion of TTX. If the patient was untreated in time, it can lead to respiratory paralysis, coma and even death. To sum up, the toxic mechanism of TTX is by blocking the transmission of nerve impulses, leading to symptoms of the nervous system, digestive system and cardiovascular system. This poisoning is acute and requires prompt treatment to avoid serious consequences.

### **4.2. Application of TTX**

Although TTX is highly toxic, it also has some important pharmacological effects at appropriate doses. TTX can block the transmission of nerve impulses, so it can be used as an anesthetic drug to some extent [7]. It can be applied to block the transmission of pain signals, thus achieving the effect of anesthesia. However, TTX is very toxic, so it needs to be used with careful mind. Typically, it's diluted to a very low concentration and then administered as a local anesthetic by a local injection that minimizes its impact on the system.

Some studies have shown that TTX can prevent kidney failure to some extent. Renal failure is usually caused by damage to the cells of the kidneys, resulting in a decreased glomerular filtration rate. TTX can inhibit certain factors that cause cell damage, thereby slowing down the damage of kidney cells. Because TTX is very toxic, when used to prevent kidney failure, the dosage needs to be strictly controlled and the guidance of doctor. TTX can block the transmission of nerve impulses, so it has a strong analgesic effect. It can be used to treat some acute pain, such as post-operative pain, trauma pain and so on [8-10]. However, due to the toxicity of tetrodotoxin, it is not usually used as a preferred analgesic. TTX could only be considered if other analgesics are ineffective [11, 12].

TTX can block the transmission of nerve impulses, so it can be used to treat patients with certain drug addictions. TTX, for example, can be used to treat opioid addiction. When patients are addicted to opioids, the medicine will affect the brain's reward system and cause the patient to have persistent

cravings. TTX can help wean patients off the drug by blocking the transmission of these nerve impulses, thereby slowing their desire.

Arrhythmia is a common heart disease that is usually caused by abnormal electrical activity in the heart. TTX can inhibit the heart's sodium ion channels, thereby slowing the heart's electrical activity to achieve a stable heart rhythm [9]. However, due to the toxicity of TTX, it is not usually used as a preferred antiarrhythmic drug. TTX could only be considered if other drugs are ineffective. TTX has a variety of pharmacological effects and can be used for anesthesia, prevention of renal failure, analgesia, drug withdrawal and anti-cardiac symptoms. However, due to its strong toxicity, it needs to be used with full care and under the guidance of doctor.

## 5. Side effects and detoxification methods

Although TTX has many potential medicinal values (Fig. 1), its side effects and toxicity cannot be ignored. In this part, it will discuss the common side effects of TTX, current detoxification methods and effects, as well as potential new detoxification methods and research directions.

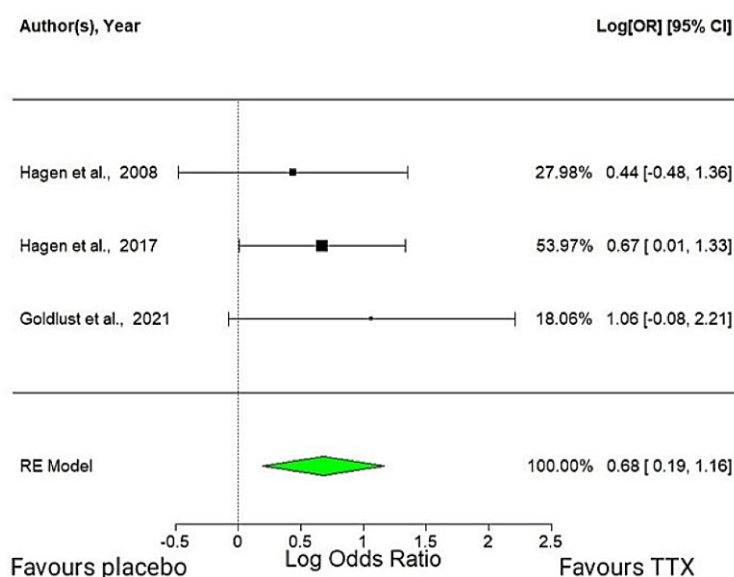


Figure 1. The analgesic effect of TTX on cancer-related pain [13]

### 5.1. Side effects

TTX acts mainly on the nervous system and can block the transmission of nerve impulses. While this can have some medicinal benefits, it can also lead to a range of neurological side effects, such as dizziness, nausea, difficulty breathing, and even coma. At the same time, TTX can affect the electrical activity of the heart, which may lead to cardiac side effects such as arrhythmia, tachycardia, and bradycardia. In addition, although some studies have shown that TTX can prevent renal failure to a certain extent, its toxicity to the kidney cannot be ignored. It can lead to urinary system side effects such as frequent urination, pain in urination, and urgency in urination.

### 5.2. Detoxification methods

For TTX poisoning, common detoxification methods mainly include gastric lavage, activated charcoal, supportive therapy, and anti-tetrodotoxin serum. Gastric lavage is the preferred method of detoxification for those who ingest tetrodotoxin for a short time. It can minimize the absorption of TTX in the intestine, thereby reducing the symptoms of poisoning. Activated carbon can absorb tetrodotoxin, thereby reducing its toxicity to the human body. Activated charcoal is usually given as soon as possible after the victim ingests tetrodotoxin. Supportive treatment involves giving enough oxygen to maintain vital signs such as breathing and carrying on heartbeat. Anti-TTX serum is a detoxification method that is currently being studied and has not been widely used.

At present, there is no specific drug for TTX poisoning. Therefore, it is an important research direction to develop new detoxification drugs that can target tetrodotoxin [10]. At the same time, understanding the mechanism of TTX can help us find new detoxification methods. For example, if it can find drugs that inhibit tetrodotoxin's effect on the nervous system, it may be likely to reduce its toxicity. In addition, improving the adsorption effect of activated carbon is also an important research direction. Because activated carbon is one of the commonly used detoxification methods at present for tetrodotoxin poisoning. But its adsorption effect is limited.

## 6. Conclusion

This research summarizes the pharmacological effects and structural characteristics of TTX and its potential applications in the medical and commercial fields. As a highly toxic neurotoxin, tetrodotoxin has the ability to block sodium ion channels, thus affecting nerve conduction, causing muscle paralysis, dyspnea and other serious symptoms. Despite its extremely high toxicity, TTX has potential medical value in analgesia, antiarrhythmia, and drug rehabilitation due to its unique pharmacological effects. However, its high toxicity also makes it face strict safety and risk control in its application. This research also faces some limitations when exploring the mechanism and potential application of TTX. The high toxicity of TTX limits its use in both clinical and laboratory settings, and researchers must take strict safety measures. The complexity and diversity of TTX make the analysis of its action mechanism relatively complex and need more in-depth studies. Moreover, although some potential applications are mentioned in this paper, these applications still need to be confirmed in rigorous scientific validation and clinical trials.

Several key directions deserve attention in future studies. First, a deep understanding of the interaction mechanism of TTX and sodium ion channels may help reveal more details of its effects and provide more precise guidance for drug development. Second, the research and development of an antidote to TTX is crucial to address toxic events so that it can reduce the risk of human health. In addition, although the pharmacological effects of TTX still need further study, its potential applications in analgesia and antiarrhythmia still need to be explored and verified. At the same time, further exploration of the distribution and transmission mechanism of TTX in the food chain is needed to understand its ecological role in nature better. As a neurotoxin with high concentration, TTX is still deepening in its pharmacological effects, structural characteristics and potential applications. Through continuous scientific exploration and rigorous experimental research, it is expected to understand the mystery of TTX better and bring more enlightenment and possibilities to human health and medical research. At the same time, in order to ensure public safety, it must also treat this high-risk toxin with scientifically and cautious attitude.

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