

A Pain-killing Poison

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*A study has shown that localized injections of the toxin found in a venomous fish, the pufferfish (*fugu*), provides a local analgesia that lasts a long time and which could be used for the treatment of chronic pain.*

EFFECTIVE, BUT DANGEROUS

The opiates (substances derived from opium) and the opioids (substances not related to opium, but which possess a similar analgesic activity) have, over the last few decades, become the principal medications used for treating pain. These molecules interact with certain receptors present in the central nervous system and prevent the pain signal from reaching the brain; consequently, even though the damage responsible for the pain remains present, the patient no longer feels the pain (or feels it with much less intensity).

This analgesic action of opiates and opioids is not, however, perfect; aside from causing nausea and constipation (two frequent secondary effects), the repeated use of these medications over long periods of time can also lead to a dependence which results in overconsumption of these drugs and an elevated risk of death by respiratory arrest. This phenomenon has become a disturbingly large problem in the United States where the deaths caused by opiate overdoses have skyrocketed over the past 15 years and are one of the major factors responsible for the reduction in lifespan observed in that country. The discovery of anti-pain medications capable of reproducing the analgesic effects of opiates while being safe to use for a prolonged time without risking dependence could thus revolutionize the treatment of pain.

FISH POISON

Because the dependence on opiates is derived from their actions on the central nervous system, one way of overcoming this problem is to locally block the nociceptive neurons, responsible for the pain signals. Along related lines, it was noted that several naturally occurring poisons specifically produce their effects by blocking the nervous influx and it was therefore suggested that these toxins could be locally injected to block the pain at its source.

The tetrodotoxin (TTX) present in the pufferfish (*fugu* in Japanese) is one of these natural toxins with potential for analgesic properties. This toxin is not produced by the fish themselves, but rather by certain bacteria which are associated with the plants that they consume, and which accumulate in the liver and reproductive organs of the pufferfish. In Japan, where *fugu* is considered by gastronomes to be a great delicacy, only chefs who have received special training in the preparation of this fish are authorized to serve it, generally in the form of sashimi slices so thin that the pattern of the serving plates can be seen through them. This precaution is essential because TTX is such an extremely toxic molecule (several thousand times more powerful than cyanide) which prevents the entry of sodium into the neurons and



causes a complete muscular paralysis by irreversibly blocking the transmission of nervous impulses.

LOCAL ANALGESIA

A team of American scientists recently tested the analgesic potential of TTX administered locally in very small quantities¹. The results obtained are very encouraging: by biochemically linking the toxin to a biodegradable polymer based on polyethylene glycol, they were first able to observe that the toxin was slowly released at the site of injection, allowing them to reduce the quantities administered and thus the risk of secondary effects caused by the toxin reaching areas not targeted by the treatment. As well, the team was able to show that the quantities of toxin used can be diminished even more by combining the toxin-polymer formulation with an agent which promotes the penetration of molecules into nerve cells and thus increases the “delivery” of the toxin to the desired site.

When the researchers injected several micrograms of this toxin formulation into the sciatic nerve of laboratory rats, they were able to achieve a complete blockage of the nerve for a period of up to three days without damage to the surrounding tissues and without apparent toxicity. According to Dr. Daniel Kohane, professor of anaesthesia at Harvard Medical School, there is no reason why a similar effect should not be seen in humans, which allows us to consider whether TTX could be used to generate local analgesia for long durations (up to three weeks) in patients suffering from chronic pain, such as cancer patients. Clinical trials dealing with the effectiveness and security of this approach should soon provide us with an answer to this question.

⁽¹⁾ Zhao C et al. Polymer-tetrodotoxin conjugates to induce prolonged duration local anesthesia with minimal toxicity. *Nat Commun.* 2019; 10(1): 2566.