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Some Hypotheses of Creation and Decomposition Processes of Tetrodotoxin in the Body of Pufferfish (Tetraodontid)

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フグ類の体内におけるテトロドトキシンの生成・分解過程に関する「仮説」

有薗眞琴

フグ毒であるテトロドトキシンの起源に関しては、これまで多くの研究が為され、現在は細菌によって合成されたものが食物連鎖を通じて取り込まれるという「外因説」が有力になっているが、それだけでは十分な説明ができない。

そこで、筆者はテトロドトキシンの特異な化学構造に着目し、その生成・分解過程に関して、「外因説」と「内因説」を組み合わせた二つの「仮説」を導いたので、その内容について報告する。

一つ目の「仮説」は、テトロドトキシンの生成過程に関するものであり、フグ毒は、甲殻類の摂食を通じて体内に取り込まれた脱皮ホルモンのエクジステロンから体内合成されるのではないかというものである。この説が正しければ、食物連鎖による生物濃縮に因らずとも一分子のエクジステロンから二分子のテトロドトキシンが効率的に生成されることになる。

二つ目の「仮説」は、テトロドトキシンの分解過程に関するものであり、フグ類は、一般に硬骨魚類ではないか若しくはあってもその役割をほとんど果たしていないとされる「オルニチン回路」を備えており、フグ毒はこの回路を通じて尿素に分解されるのではないかというものである。この説が正しければ、テトロドトキシンは、従来言われてきた外敵に対する「防御機能」や産卵期における雄フグに対する「フェロモン機能」に加え、「浸透圧調整機能」としても重要な役割を果たしている可能性が出てくる。

Key words : Puffer (Tetraodontid); Tetrodotoxin (TTX) ; Ecdysterone; Creation and decomposition processes

Although there have been many discussions on the origin of tetrodotoxin (TTX) and its role in the body of pufferfish, a clear explanation has not been made.

Then I attempt to make these problems clear on the following hypotheses aiming at a unique chemical constitution of TTX, that is the cage compound with a lactone ring, a guanidine radical and five hydroxyl groups *etc* (Fig.1).

In this paper, the hypothesis is divided into two sections: one is a process of the creation of TTX and the other is a process of the decomposition of it. The former is based on the hypothesis that TTX originates in ecdysterone (a molting hormone of crustaceans, Fig.2) through the feed, the latter is based on the hypothesis that TTX is decomposed into the urea by "Ornithine cycle" *in vivo*.

In spite of the theory that teleost fishes generally have not "Ornithine cycle" for lacking of necessary enzymes[1], if pufferfish exceptionally had the cycle according to the hypothesis, it woud become easy to explain the metabolic process of TTX in the body of the fish.

Thus the main role of TTX for the pufferfish may be explained not only as a protection against enemies or a male-attracting pheromone[2] but also a substance concerned in an osmotic regulation.

Tetrodotoxin (TTX) ; $C_{11}H_{17}O_8N_3$

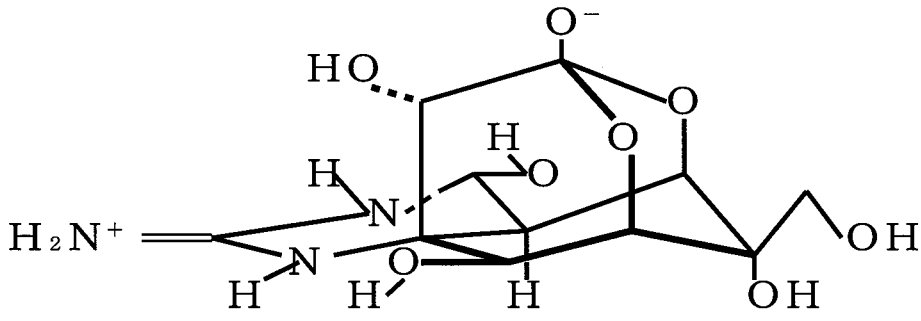


Fig.1. The structural formula of tetrodotoxin (TTX) .

Ecdysterone ; $C_{27}H_{44}O_7$
molting hormone of crustaceans

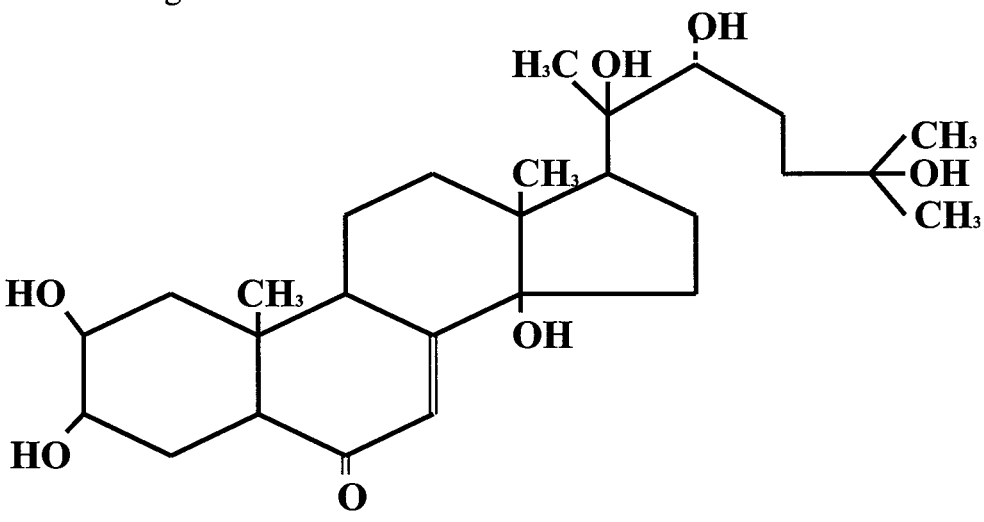


Fig.2. The structural formula of Ecdysterone.

Hypothesis − I

In this section, I suggest the hypothesis that TTX ($C_{11}H_{17}O_8N_3$) is created from ecdysterone (a molting hormone of the crustaceans; $C_{27}H_{44}O_7$) in the body of pufferfish and the hormone is taken through feeding on crustaceans.

On the above hypothesis, a process of the creation of TTX *in vivo* will be shown as follows in the rough (Fig.3).

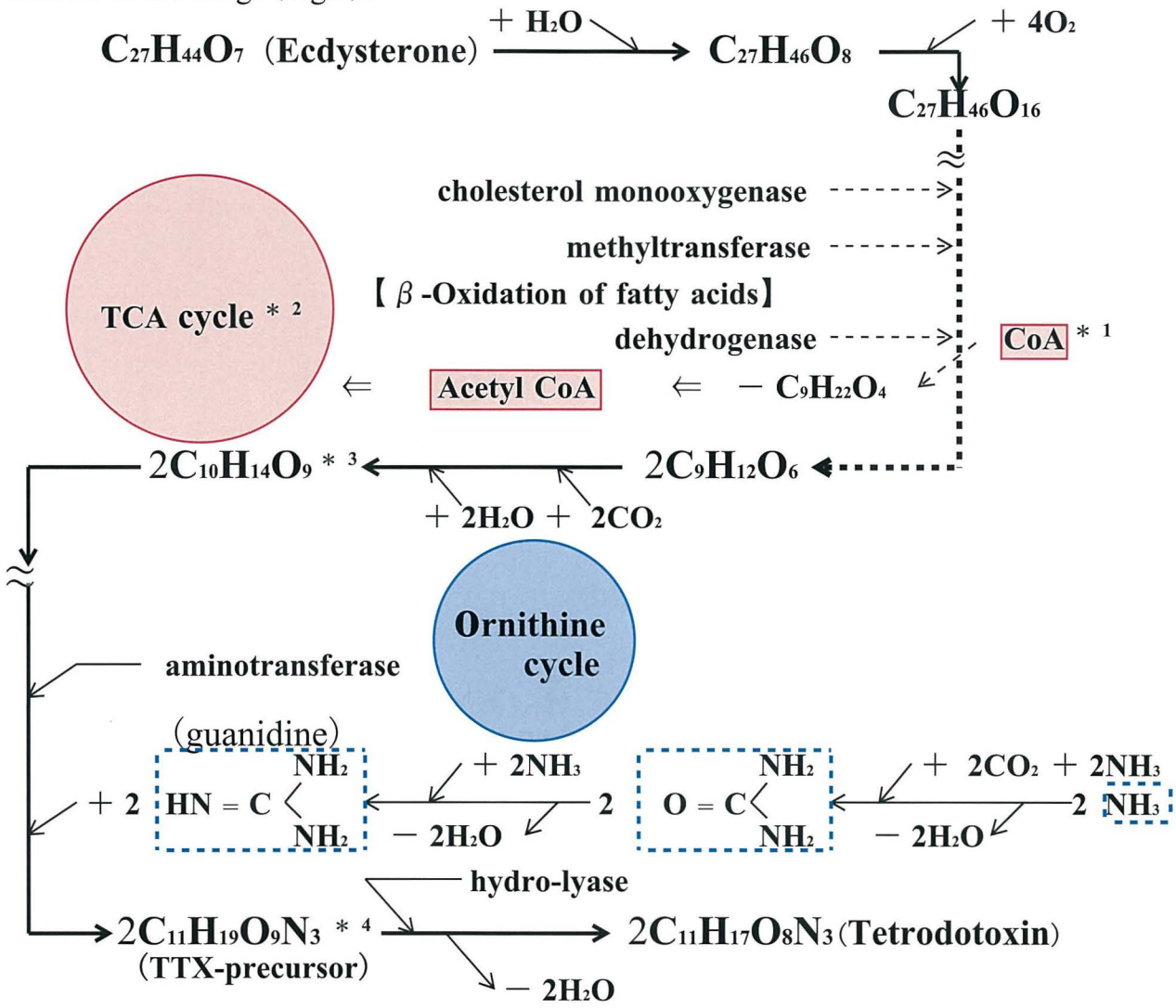


Fig.3. A hypothetical process of the creation of tetrodotoxin (TTX) *in vivo*.

＊1 coenzyme A (CoA)
＊2 tricarboxylic acid cycle (TCA cycle)
＊3 sialic acid
＊4 similar substance of N-acetylneuraminic acid

Hypothesis — Ⅱ

In this section, I suggest the hypothesis that TTX is decomposed into the urea ($CO(NH_2)_2$) by "Ornithine cycle" and TTX is concerned with an osmotic regulation in the body of pufferfish.

On the above hypothesis, a process of the decomposition of TTX *in vivo* will be shown as follows in the rough (Fig.4).

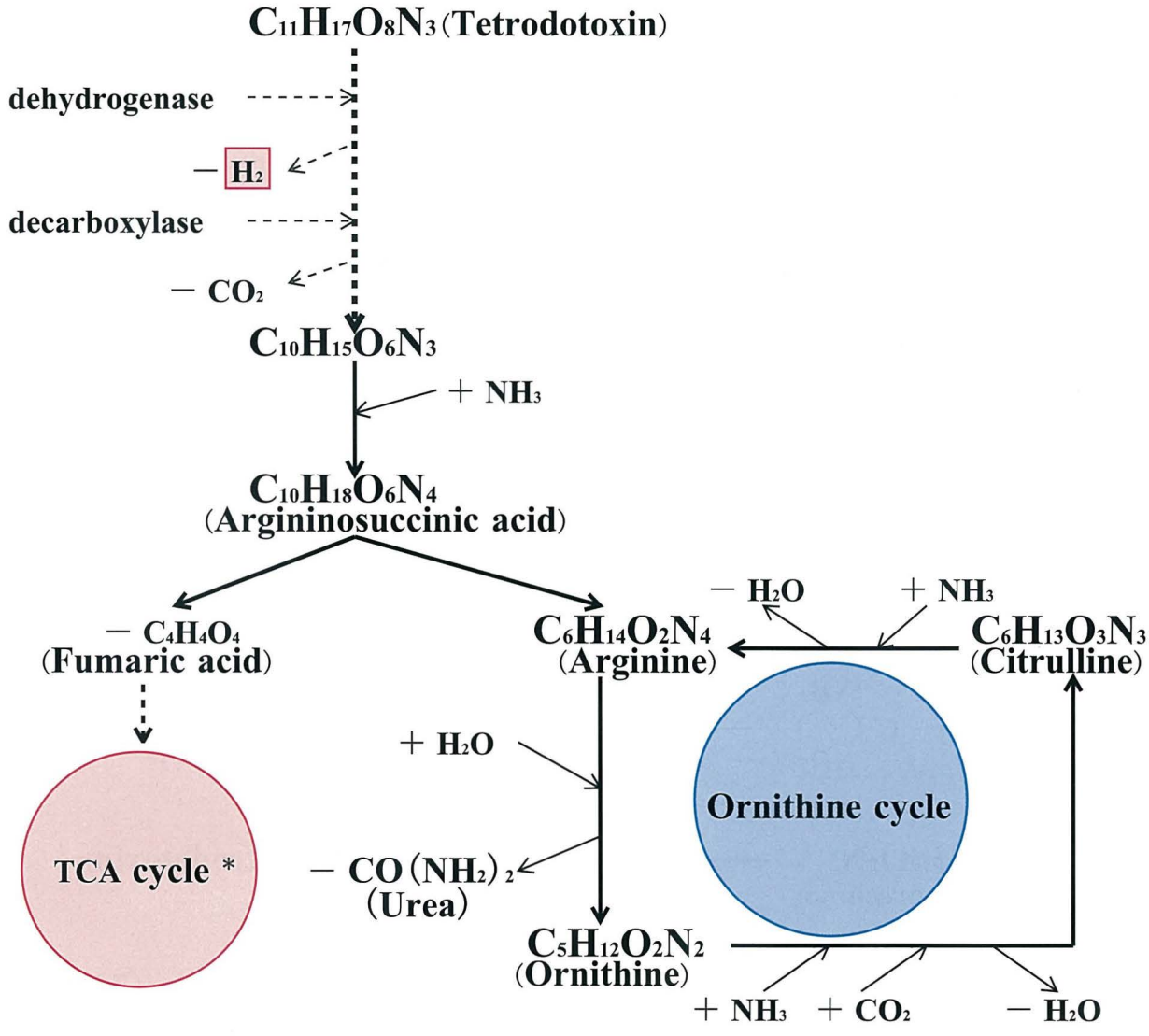


Fig.4. A hypothetical process of the decomposition of tetrodotoxin (TTX) *in vivo*.

* tricarboxylic acid cycle (TCA cycle)

Although the substance of this paper might be an unrealistic assumption for the present, but it becomes easy for me to answer various questions concerning TTX by means of the above hypotheses; that is, "where does TTX rise ?", "why does pufferfish have TTX ?" , "why does not the cultured pufferfish have TTX ?" , "why does not the pufferfish die of TTX-poisoning ?" and so on.

There is not sufficient evidence to prove these questions by the accepted theory of " external cause" , a bacterial synthesis based on the food chain[3], because we never had any experience in the death of fishes caused by TTX-poisoning in nature, nevertheless it must happen frequently.

The other side, the hypotheses in this paper are made by a joint theory of "external cause " and "internal cause" in a sense, because TTX is created from ecdysterone through the feeding on crustaceans, and is decomposed into the urea by "Ornithine cycle " *in vivo* as occasion demands.

At the begining when the hypothesis was suggested, I considered that the origin of TTX must exist widely in nature, and I marked ecdysterone with the chemical constitution, because ecdysterone is similar to TTX with regard to the existence of many hydroxyl groups (*i.e.* the former is six, the latter is five).

As a result of investigations, I have reached the above unprecedented hypotheses .

If the "**Hypothesis- I** " wouldn't be wrong, pufferfish can get efficiently two molecules of TTX from one molecule of ecdysterone without bioaccumulation, and it will answer the question, "why does not the cultured pufferfish have not TTX ?" ; because the cultured pufferfish are given the food without live crustaceans (ecdysterone) in the cage. Furthermore, if the "**Hypothesis- II** " wouldn't be wrong, it will be supposed that one of the main role of TTX is an osmotic regulation as well as a protection against enemies and a male-attracting pheromone for pufferfish, and it will answer the question, "why does not the pufferfish die of TTX-poisoning" , because there may be TTX-metabolism in pufferfish.

Anyhow, it is necessary to investigate whether the hypotheses used in the theory are correct or not in the future.

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