

# Activation of the 5-hydroxytryptamine Degradation System in Cells and Organ Injury

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## Abstract

This paper summarizes the research results of Fu et al. on the pathological mechanism of organ injury. A hypothesis was proposed that "organ injury is a consequence of the activation of the 5-hydroxytryptamine degradation system (5DS) axis in cells". The basic composition of the 5DS axis in cells and the principle of its activation leading to cell lesions were determined. The possibility of treating various organ injury diseases in clinical practice by inhibiting the 5DS axis is discussed.

**Keywords:** Apoptosis, Cell lesion, Inflammatory cytokines, MAPK pathway cell signaling, Mitochondrial damage, Reactive oxygen species

## Commentary

Vascular blockage-induced injury to the heart, brain, or other organs is a common clinical disease. If blood flow is blocked due to thrombosis, atherosclerosis, or other reasons in the internal blood vessels of an organ, it causes local tissue ischemia, leading to stroke, myocardial infarction, acute kidney injury, and other organ diseases. Studies have shown that restoration of the blood supply after ischemia, known as ischemia-reperfusion, can lead to severe organ injury, known as ischemia-reperfusion injury (IRI). A study of myocardial ischemia-reperfusion injury (MIRI) showed that reactive oxygen species (ROS) produced by myocardial cells during reperfusion play a crucial role in the occurrence and development of MIRI [1,2]. ROS can cause oxidative stress, inflammation, and apoptosis of cells, leading to cardiomyocyte lesions [3,4]. Our studies have revealed that the generation of ROS during IRI was due to the activation of the 5-hydroxytryptamine (5-HT) degradation system (5DS) in damaged cells [5,6]. There is a 5DS in cells, which consists of the 5-HT<sub>2A</sub> receptor (5-HT<sub>2A</sub>R), 5-HT synthases (tryptophan hydroxylase and aromatic amino acid decarboxylase) and the 5-HT degrading enzyme monoamine oxidase A (MAO-A) [5-8], which is called the 5DS axis. In these studies, we found that

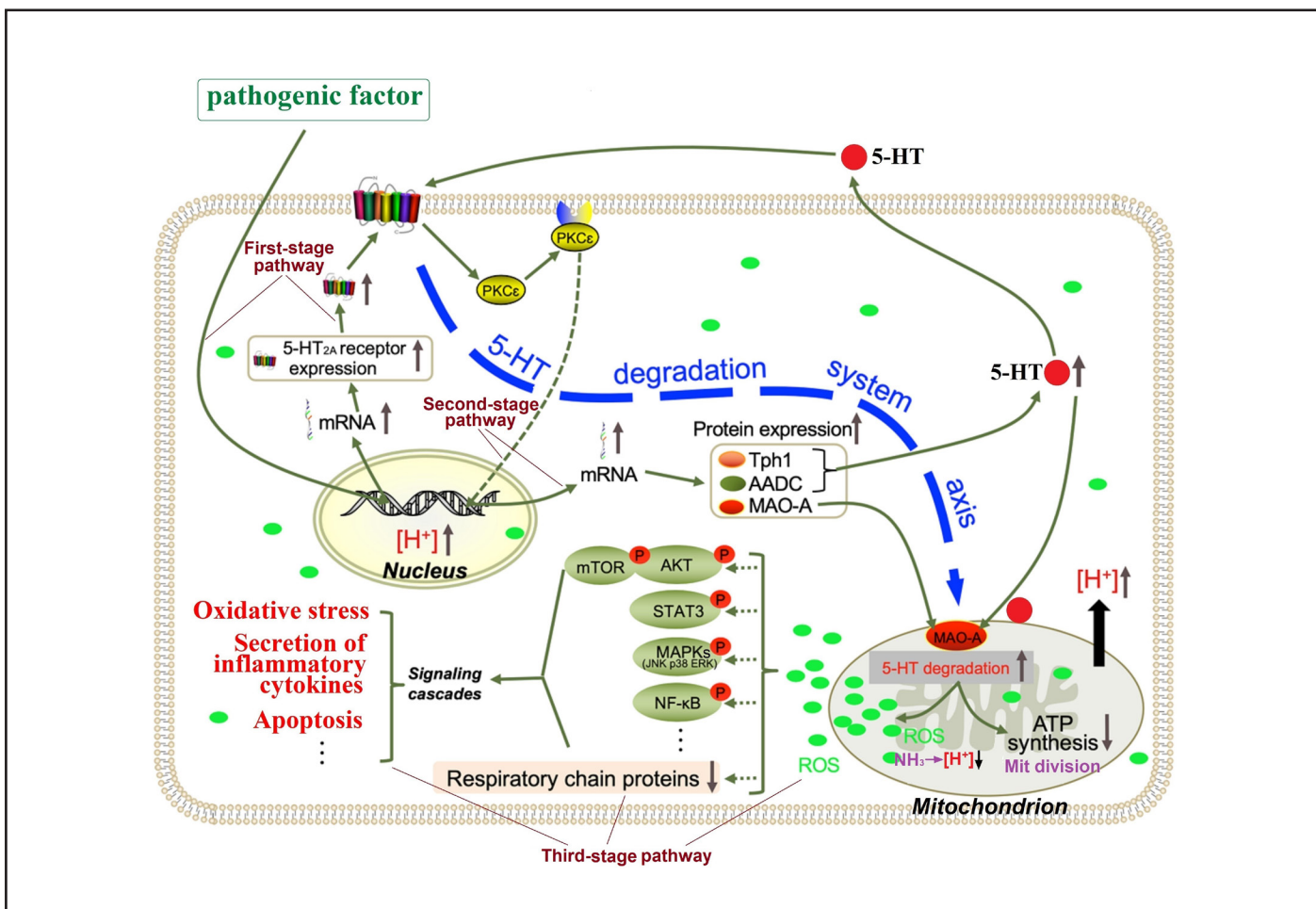
the 5DS axis was only activated in response to the pathogenic factors IRI and carbon tetrachloride, and was not activated in normal cells. It was confirmed that mitochondrial damage and cell lesions induced by pathogenic factors was due to excessive activation of the 5DS axis.

Interestingly, we found that various pathogenic factors activated the 5DS axis and led to ROS production in mitochondria. In addition to IRI [5,6], some chemical toxins (carbon tetrachloride, cisplatin) [9,10] and lipids [11] were pathogenic factors. Moreover, the mechanism by which pathogenic factors induce mitochondrial ROS production to lead to mitochondrial damage and cell lesions is due to the activation of the 5DS axis in cells. We detected that pathogenic factors induced cell damage through three-stage sequential intracellular pathways [5,7,8]: (1) first, pathogenic factors act on the nucleus through an intracellular pathway to promote the expression of 5-HT<sub>2A</sub>R genes and proteins, leading to the activation of 5-HT<sub>2A</sub>R; and (2) second, activated 5-HT<sub>2A</sub>R activates protein kinase C $\epsilon$  (PKC $\epsilon$ ), which further acts on the nucleus through an intracellular pathway to promote the expression of 5-HT synthase and MAO-A genes and proteins, leading to increases in 5-HT synthesis and

5-HT degradation. During the 5-HT degradation process, which is catalyzed by MAO-A, ROS, and ammonia ( $\text{NH}_3$ ) are generated in mitochondria. Since MAO-A is located in the outer mitochondrial membrane,  $\text{NH}_3$  could reduce the concentration of  $\text{H}^+$  in the mitochondrial intermembrane space ( $\text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+$ ) and increase the concentration of  $\text{H}^+$  in the cytoplasm and nucleus, thereby resulting in high ROS levels and abnormal pH values in the cell. (3) The third-stage pathway is activated by high levels of ROS and abnormal pH in cells, leading to a series of intracellular changes associated with mitochondrial damage (inhibition of respiratory chain, reduction of ATP synthesis, mitochondrial division, etc.), cell lesions (oxidative stress, secretion of inflammatory cytokines, apoptosis, etc.), and the activation of a series of intracellular signaling pathways related to cell lesions. We hypothesize that the first- and second-stage pathways are relatively simple, while the third-stage pathway is complex. We found that the activation of the MAPKs, STAT3, NF- $\kappa$ B and AKT-mTOR signaling pathways, the activation of the apoptosis signaling pathway, and the control of the respiratory chain, ATP synthesis and division in mitochondria, are all pathways in the third category.

A schematic diagram is shown in **Figure 1**.

The 5DS axis can be found in the cells in various organs, is affected by pathogenic factors and leads to organ injury when activated. For example, macrophages become foam cells in response to lipids and are deposited in the vascular wall to cause atherosclerosis [11]; myocardial cells are damaged by ischemia-reperfusion, leading to MIRI [5]; carbon tetrachloride injury to hepatocytes leads to acute liver injury [9]; and renal tubular epithelial cells are injured by ischemia-reperfusion or cisplatin, resulting in acute kidney injury [6,10]. Moreover, histopathological examination showed that cells with lesions in the organ are inevitable cells, in which the 5DS axis is activated, while cells without an activated 5DS axis do not undergo cell lesions [5-7,10]. Therefore, we propose a hypothesis that the pathological mechanism of organ injury is due to the activation of the 5DS axis by pathogenic factors. If any form of pathogenic factor could activate the 5DS axis in cells within an organ, it would lead to organ injury. We have found that inhibiting the 5DS axis, such as by inhibiting 5-HT<sub>2A</sub>R, simultaneously inhibiting 5-HT<sub>2A</sub>R and 5-HT synthesis,



**Figure 1.** Under the induction of pathogenic factors, the 5DS axis is involved in the development of mitochondrial damage and cell lesions via three-stage sequential intracellular pathways. Tph1: Tryptophan hydroxylase 1; AADC: Aromatic L-amino acid Decarboxylase; MAO-A: Monoamine oxidase-A; ROS: Reactive Oxygen Species; Mit: Mitochondrion.

or inhibiting MAO-A activity, could effectively inhibit atherosclerosis [11], myocardial injury [5], liver injury [9], and kidney injury [6,10] caused by different pathogenic factors.

## Prospects

The first- and second-stage pathways need to be clarified. We have shown that IRI regulates the gene expression of 5-HT<sub>2A</sub>R by activating platelet activating factor receptor, which is located in the first-stage pathway [5], while 5-HT<sub>2A</sub>R regulates the gene expression of 5-HT synthases and the MAO-A by activating PKC $\epsilon$ , which is located in the second-stage pathway [5,8]. It can be inferred that the second- and third-stage pathways of cell injury induced by various pathogenic factors are the same, while the first-stage pathway may be different, which needs to be confirmed by further research.

Based on this understanding, we can treat organ injury caused by various pathogenic factors in different organs by blocking the second-stage pathway. It is possible to find a universal treatment method for clinical organ injury-related diseases. The animal experiments that were performed by us support this view. Our findings provide a new approach for the treatment of organ injury-related diseases in clinical practice. Inhibiting the 5HT axis may be a clinically effective method for treating organ injury-related diseases, and it has universal significance.

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