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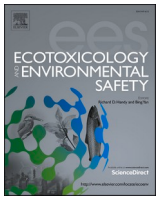

H_2S exposure induces cell death in the broiler thymus via the ROS-initiated JNK/MST1/FOXO1 pathway☆

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ABSTRACT

Hydrogen sulfide (H_2S) is a common toxic gas in chicken houses that endangers the health of poultry. Harbin has a cold climate in winter, and the conflict between heat preservation and ventilation in poultry houses is obvious. In this study, we investigated the H_2S content in chicken houses during winter in Harbin and found that the H_2S concentration exceeded the national standard in individual chicken houses. Then, a model of H_2S exposure was established in an environmental simulation chamber. We also developed a NaHS exposure model of chicken peripheral blood lymphocytes in vitro. Proteomics analysis was used to reveal the toxicology of thymus injury in broilers, the FOXO signaling pathway was determined to be significantly enriched, ROS bursts and JNK/MST1/FOXO1 pathway activation induced by H_2S exposure were detected, and ROS played an important switch role in the JNK/MST1/FOXO1 pathway. In addition, H_2S exposure-induced thymus cell death involved immune dysregulation. Overall, the present study adds data for H_2S contents in chicken houses, provides new findings for the mechanism of H_2S poisoning and reveals a new regulatory pathway in immune injury.

1. Introduction

Hydrogen sulfide (H_2S) is an acute toxic inorganic gas, and its production in chicken houses is inevitable. H_2S mainly originates from the decomposition of sulfur-containing organic matter in feces. When chickens feed on sulfur-containing amino acids (such as cystine, cysteine and methionine) and encounter digestive system diseases, a large amount of H_2S can also be produced (Ni et al., 2021; Wang et al., 2011). In rural chicken production, because farmers often disregard environmental sanitation control in chicken houses, harmful gases often accumulate in the houses, which substantially reduces the economic benefits of chicken breeding. In northern China, the climate is cold in winter, and the conflict between heat preservation and ventilation in poultry houses is obvious. Insufficient ventilation can easily lead to an increase in H_2S concentration in poultry houses. To date, many studies have discussed the injurious effects of excessive H_2S exposure in chicken houses, including the most direct impact on the respiratory system (Song et al., 2021), as well as injury to other solid organs (Chi et al., 2020). In addition, the injury mechanisms of H_2S have also been widely studied by researchers, including apoptosis, necroptosis, pyroptosis, and inflammation (Lewis and Copley, 2015; Lim et al., 2016). Quantitative assessment methods of oxidative stress include indirect determination of antioxidant and enzyme levels in the reactive oxygen species (ROS) elimination system or direct detection of ROS levels at the cellular level (Yiming et al., 2021b; Zhang et al., 2020). H_2S exposure can induce an ROS burst, decrease antioxidative activities (Khattak et al., 2021), and disturb the homeostasis of the immune system in broilers.

The thymus is the site where T cells and B cells differentiate, develop and mature and is one of the important organs maintaining the immune homeostasis of broilers. Thymus injury caused by external stimuli implies an imbalance in immune homeostasis (Beamer et al., 2019). Many mechanisms can lead to immune system damage, and immune dysregulation is arguably the most relevant mechanism of injury (Azizi et al., 2016). Immune dysregulation occasionally occurs due to stimulation by unfavorable external factors, such as heavy metal exposure (arsenic (Huang et al., 2019) and manganese (Chen et al., 2018)), pathogenic microbial infections (Channappanavar and Perlman, 2017), and pathological conditions (Barreyro et al., 2018). In these processes, cell death, including apoptosis, primary and secondary necrosis, necroptosis, pyroptosis and autophagy, plays a role in tissue injury and immune

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