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Sulforaphane Inhibits Paraquat-Induced Oxidative Stress by Activating the Nuclear Factor Erythroid 2-Related Factor 2 Signaling Pathway

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SUMMARY*. Paraquat (PQ) is a widely used herbicide that can cause acute oxidative lung injuries with high mortality. The nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway is essential for cellular defense against oxidative stress. Sulforaphane (SFN) is common isothiocyanate with stong antioxidative effects. We aimed to investigate the regulatory role of Nrf2/ARE pathway and the therapeutic effects of SFN in mice model with PQ-induced lung injury. Mice were randomly divided into control, PQ, PQ+SFN groups. The histological changes in lung tissues were compared by HE staining. The expression of cytoprotective genes HO-1 and NQO1 was determined by flow cytometry, western blot and RT-PCR. The degree of oxidative stress was measured by 8-OHdG ELISA. Extensive inflammatory cell infiltration was observed in the lung tissues in PQ group. The alveolar septum were enlarged and congested with red blood cells. The HO-1 and NQO1 expression was increased in a time-dependent manner ($P < 0.05$). The 8-OHdG level was initially increased at 12h after PQ exposure but started to decrease thereafter. The SFN intervention significantly promoted the HO-1 and NQO1 expression ($P < 0.05$). The 8-OHdG level in PQ+SFN group was significantly reduced compared with PQ group ($P < 0.05$). Our study has confirmed the important regulatory role of the Nrf2/ARE pathway in the defense against PQ-induced acute lung injury, which is triggered to gradually reduce the intracellular PQ-induced oxidative stress. SFN treatment can effectively alleviate the oxidative injury due to PQ pulmonary toxicity by activating the Nrf2/ARE pathway.

RESUMEN. El paraquat (PQ) es un herbicida ampliamente utilizado que puede causar lesiones pulmonares oxidativas agudas con alta mortalidad. El factor nuclear erythroid 2-factor relacionado 2 (Nrf2)/elemento antioxidante respuesta (ARE) es esencial para la defensa celular contra el estrés oxidativo. El sulforáfano (SFN) es un isotiocianato común con fuertes efectos antioxidantes. Nuestro objetivo fue investigar el papel regulador de la vía Nrf2/ARE y los efectos terapéuticos de SFN en el modelo de ratones con lesión pulmonar inducida por PQ. Los ratones se dividieron aleatoriamente en grupos control, PQ, PQ + SFN. Los cambios histológicos en los tejidos pulmonares se compararon mediante tinción HE. La expresión de los genes citoprotectores HO-1 y NQO1 se determinó mediante citometría de flujo, western blot y RT-PCR. El grado de estrés oxidativo se midió mediante 8-OHdG ELISA. Se observó una infiltración extensa de células inflamatorias en los tejidos pulmonares en el grupo PQ. El tabique alveolar estaba aumentado de tamaño y congestionado con glóbulos rojos. La expresión de HO-1 y NQO1 se incrementó de una manera dependiente del tiempo ($P < 0,05$). El nivel de 8-OHdG aumentó inicialmente a las 12 h después de la exposición a PQ, pero comenzó a disminuir a partir de entonces. La intervención de SFN promovió significativamente la expresión de HO-1 y NQO1 ($P < 0,05$). El nivel de 8-OHdG en el grupo PQ + SFN se redujo significativamente en comparación con el grupo PQ ($P < 0,05$). Nuestro estudio ha confirmado el importante papel regulador de la vía Nrf2/ARE en la defensa contra la lesión pulmonar aguda inducida por PQ, que se desencadena para reducir gradualmente el estrés oxidativo inducido por PQ intracelular. El tratamiento con SFN puede aliviar eficazmente la lesión oxidativa debida a la toxicidad pulmonar PQ activando la vía Nrf2/ARE.

KEY WORDS: lung injury, Nrf2/ARE pathway, paraquat poisoning, sulforaphane.

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