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Ferrous iron (Fe^{2+}) increases pro-inflammatory cytokine production of peripheral blood mononuclear cells in response to influenza A virus (IAV)

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Influenza A virus (IAV) remains a constant pandemic threat, with the WHO estimating that IAV causes 3–5 million cases of severe illness resulting in 250,000 to 500,000 deaths each year. Previous studies have implicated high systemic levels of iron with increased IAV disease severity, but the nature of the association remains unknown.(1) In particular, the roles of ferrous or heme iron (Fe^{2+}), found in meat, compared to ferric (Fe^{3+}) or non-heme iron, found primarily in plants, has not been previously investigated in the context of IAV infection. In this study we examined the effects of increased levels of ferrous iron, in the form of ferrous sulphate (FS), and ferric iron, in the form of ferric ammonium citrate (FAC), on pro-inflammatory and anti-viral immune responses to IAV in peripheral blood mononuclear cells (PBMCs) to better understand how increased levels of different forms of iron affect immune responses to IAV. PBMCs were isolated from blood collected from healthy participants ($n = 5$). PBMCs were then cultured in the presence of FS (50 μM), FAC (50 μM) or media control for 3 hours, then infected with IAV H1N1pdm09 (multiplicity of infection 0.1) for 24 hours. Cell culture supernatant was then collected and assayed by Enzyme-linked Immunosorbent Assay (ELISA) for concentration of the inflammatory mediators interleukin (IL)-1β, IL-6, interferon (IFN)-α2, and IFN-γ. Data was analysed using Friedman test, with Dunn's multiple comparisons where appropriate. Pre-treatment with FS significantly increased the production of pro-inflammatory cytokines IL-6 (39.58 (31.14, 162.1) v. 74.34 (46.99, 387.40) pg/mL; $p = 0.034$) and IL-1β (4.28 (1.07, 22.87) v. 7.64 (6.23, 79.56) pg/mL; $p = 0.013$) as well as production of IFN-α2 (636.3 (407.0, 1443) v. 782.5 (627.5, 1708.0) pg/mL; $p = 0.013$) of PBMCs infected with IAV. Pre-treatment with FAC, however, did not alter production of pro-inflammatory cytokines or interferons from PBMCs in response to IAV infection. Ferrous iron (Fe^{2+}), but not ferric iron (Fe^{3+}), increased the production of both pro-inflammatory and anti-viral mediators by PBMCs in the context of IAV infection. Increased production of damaging pro-inflammatory mediators in response to IAV may implicate ferrous iron in worsened disease outcomes, however this may be nullified by the increased production of the antiviral mediator IFN-α2. Further research is needed to elucidate the role of ferrous iron in IAV infection and whether it may be a potential therapeutic target for improving outcomes in respiratory viral disease.

References

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