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# Activation of the hexosamine pathway causes oxidative stress and abnormal embryo gene expression: involvement in diabetic teratogenesis.

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## Abstract

BACKGROUND: Oxidative stress is critical to the teratogenic effects of diabetic pregnancy, yet the specific biochemical pathways responsible for oxidative stress have not been fully elucidated. The hexosamine pathway is activated in many tissues during diabetes and could contribute to oxidative stress by inhibiting the pentose shunt pathway, thereby diminishing production of the cellular antioxidant, reduced glutathione (GSH).

METHODS: To test the hypothesis that activation of the hexosamine pathway might contribute to the teratogenic effects of diabetic pregnancy, pregnant mice were injected with glucose, to induce hyperglycemia, or glucosamine, to directly activate the hexosamine pathway. Embryo tissue fragments were also cultured in physiological glucose, high glucose, or physiological glucose plus glucosamine, to test effects on oxidative stress and embryo gene expression.

RESULTS: Glucosamine increased hexosamine synthesis and inhibited pentose shunt activity. There was a trend for transient hyperglycemia to have the same effects, but they did not reach statistical significance. However, both glucose and glucosamine significantly decreased GSH, and increased oxidative stress, as indicated by 2',7'-dichloro-dihydrofluorescein fluorescence. Glucose and glucosamine inhibited expression of Pax-3, a gene required for neural tube closure both in vivo and in vitro, and increased neural tube defects (NTDs) in vivo; these effects were prevented by GSH ethyl ester. High glucose and glucosamine inhibited Pax-3 expression by embryo culture, but culture in glutamine-free media to block the hexosamine pathway prevented the inhibition of Pax-3 expression by high glucose.

CONCLUSIONS: Activation of the hexosamine pathway causes oxidative stress through depletion of GSH and consequent disruption of embryo gene expression. Activation of this pathway may contribute to diabetic teratogenesis.

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