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CAFFEINE INTAKE AND RISK OF NEURAL TUBE DEFECTS: AUTHOR RESPONSE TO CORRESPONDENCE

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To the Editor

Thank you for the opportunity to respond to the letter from Cavalli et al. (2010) regarding our manuscripts on caffeine and risk for neural tube defects (NTDs) (Schmidt et al., 2009; Schmidt et al., 2010). We appreciate the authors' suggestion for an alternative mechanism behind the association between caffeine and increased risk for NTDs that involves inositol metabolism. The effect of caffeine on IP3-related calcium channels and ryanodine receptors appears to be a biologically relevant pathway through which caffeine could affect calcium regulation and ultimately lead to NTDs.

Typically, high concentrations of caffeine (1–5 mM) are necessary to alter the function of IP3R and RyRs (Bezprozvanny et al., 1994), which would require mothers to consume very large amounts of caffeine to raise blood levels sufficiently to invoke IP3R and RyR mechanisms in the developing fetus. This would not be consistent with our association between even low levels of caffeine intake and NTDs. However, hundreds of known mutations in RyR genes and their accessory proteins significantly enhance their sensitivity to caffeine (Cerrone et al., 2009; Zhou et al., 2009). Given additional genetic susceptibility, even low levels of caffeine exposure during critical periods of development could predispose a fetus to NTDs. Moreover, several environmental agents of concern to human health sensitize RyRs in an allosteric manner (Pessah et al., 2010) and theoretically could amplify the effects of low-level caffeine exposure. We suggest that these mechanisms be tested in mouse models that express human mutations of RyRs.

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In addition, most cells express both IP3Rs and RyRs, and the calcium stores they regulate largely overlap. As described by Cavalli et al. (2010), caffeine acts to sensitize RyRs, thereby promoting the opening of calcium channels, also known as RyR “leakiness.” Caffeine is an antagonist of adenosine receptors (ARs), and the stimulant actions are produced primarily through blocking the depressant actions of adenosine through the A1 and A2A ARs (Fredholm and Jacobson, 2009). This action combined with caffeine-sensitized RyRs could work synergistically to produce overstimulation of cells at lower caffeine concentrations. With chronic exposures to caffeine, phosphoinositide precursors could be depleted, especially if dietary inositol was limited. This in combination with the depleted calcium stores (due to leaky RyRs) and the direct inhibition IP3R could eventually disable the major calcium signaling pathways and could potentially be prevented/reversed with *myo*-inositol supplementation. Again, mouse models might be used to test whether affects of caffeine in susceptible mice can be negated with *myo*-inositol supplementation.

Although classifying NTDs into folate-sensitive and folate-resistant would have been ideal for teasing apart etiologic pathways, information was not available to do this in the National Birth Defects Prevention Study. In stratified analyses across maternal folic acid supplement intake, we did not observe meaningful differences in the effects of caffeine for combined NTDs. The lack of interaction effects with folic acid appeared counter to our hypothesized homocysteine mechanism, as one would expect folic acid to protect against this pathway. However, it would be congruent with the mechanism proposed by Cavalli and colleagues (2010). We believe the mechanism the authors proposed has scientific merit, and we agree with their call for further studies.

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