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VITAMIN B6 IS REQUIRED FOR *DROSOPHILA* CHROMOSOME INTEGRITY

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Chromosome aberrations (CAs) are one of the major contributing factors to carcinogenesis. Recent work has shown that micronutrients such as folic acid and vitamins B6 and B12 play important roles in the maintenance genome integrity and cancer prevention. We isolated mutations in the *Drosophila dPdxk* gene that encodes pyridoxal kinase, a highly conserved enzyme required for vitamin B6 (PLP) biosynthesis. *dPdxk* mutants exhibit elevated CA frequencies (~ 6% *vs* 0.5 % in controls) in *Drosophila* larval brain cells. Cytological analysis of brain preparations from *dPdxk* mutant larvae grown in food supplemented with PLP showed complete rescue of the CA phenotype. In addition, wild type larvae treated with vitamin B6 antagonists (4-deoxypyridoxine hydrochloride, penicillamine, cycloserine or isonazid) displayed high CA frequencies (ranging from 3 to 19%), confirming that PLP plays an essential role in the maintenance of genome integrity. Surprisingly, *dPdxk* mutant larvae and isolated brains grown in the presence of D-glucose (1%) showed a strong increase in the frequency of CAs (from 6% to 30%); D-glucose treatment of wild type larvae and brains did not result in detectable effects on chromosome integrity. These results indicate that in absence of PLP, D-glucose is genotoxic. Larval brains and hemolymph of *dPdxk* mutants showed a higher glucose concentration than their wild type counterparts. We also observed that mitotic spindles of *dPdxk* mutants are resistant to colchicine-induced microtubule depolymerization, an effect due to tubuline glycosilation. Together, our results show that an elevated intracellular concentration of glucose has clastogenic effects that are likely to result from AGEs (Advanced Glycation End-products) accumulation. Consistent with this hypothesis, *dPdxk* mutant brains treated with both glucose and a-lipoic acid (a well-known AGE inhibitor) showed fewer CAs than brains treated only with glucose. The clastogenic effect of glucose in the absence of vitamin B6 is evolutionarily conserved. Inactivation of *PDXK* in human fibroblasts and HeLA cells by either RNAi or chemical inhibitors resulted in chromosome breakage, which was potentiated by glucose addition. These results suggest that patients with vitamin B6 deficiency or treated with vitamin B6 inhibitors may suffer chromosomal damage when their blood sugar is too high.