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Combination of colorings, common food additives derails nerve cell growth, signalling

Common food additives and colorings can interact in ways that are highly dangerous to developing brain cells, according to new research from Britain.

Karen Lau and colleagues first studied the individual effects of two flavor enhancers, L-glutamic acid (MSG) and aspartame, and two food colorings, "brilliant blue" and "quinoline yellow." (Brilliant blue is used in the U.S. but banned by most countries in Europe, while quinoline yellow is banned in the U.S., Australia, and Norway, but is used elsewhere. Both L-glutamic acid and aspartame are widely used in the U.S. and elsewhere.) The researchers then tested the effects of two combinations—MSG mixed with brilliant blue, and aspartame mixed with quinoline yellow—using mouse neuroblastoma cells as a model for neurons.

Lau and colleagues found that individually, brilliant blue was the most potent inhibitor of neural growth, followed by L-glutamic acid, quinoline yellow and aspartame. The additive mixtures had a powerful synergistic effect, stunting nerve cell growth to a far greater degree than individual toxicities would suggest—up to four times as much for MSG/brilliant blue, and up to seven times as much for aspartame/quinoline yellow. "The results indicate," the researchers say, "that both combinations are potentially more toxic than might be predicted from the sum of their individual compounds." Further analysis showed that the effects of MSG and aspartame, but not the colorings, were consistent with NMDA-receptor excitotoxicity (overstimulation of NMDA receptors on neurons, leading to cell damage).

Lau and colleauges also analyzed the additive and coloring content of five common British snack and drink products, and calculated the possible exposures for a 10-kilogram (22-pound) child based on additive contents and estimated gut absorption. According to their data, the researchers say, additive concentrations high enough to cause nerve growth inhibition could theoretically be reached by ingesting a typical snack and drink.

> Lau and colleagues found that combinations of additives had a powerful synergistic effect, stunting nerve cell growth to a far greater degree than each individual substance did.

Food colorings, MSG, and aspartame are common ingredients of foods eaten by young children, who are the most vulnerable, the researchers say, to the toxic effects of these substances. During the "brain growth spurt" period that children experience between the sixth month of gestation and several years after birth, they say, "Cell proliferation, migration, differentiation and synapse formation progress in a tightly programmed and orderly fashion. Interference with any stage of this cascade of events may alter normal progression of sub-

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"Didn't I just get an issue?"

Yes! The astonishing response to our DAN! Project kept us so busy this year that we've been overwhelmed for the past few months. We're sending you back-to-back issues of the ARRI now, to make up for falling a bit behind schedule... and we thank you for your patience!

More clues point to oxidative stress, B12 deficits in autism

A new study adds to evidence linking impaired B12 metabolism and oxidative stress to autism (see related editorial on page 3).

Sergiu Pasca and colleagues analyzed homocysteine levels and other biomarkers in 12 autistic children and 9 controls. They report that:

—Autistic children had significantly higher plasma total homocysteine levels than controls. The amino acid homocysteine is a byproduct of methionine metabolism, and is "recycled" back into methionine with the aid of vitamin B12 and folate. If this process is impaired, toxic levels of homocysteine can accumulate in the body. The researchers speculate that in autism, high homocysteine levels could impair neuronal plasticity and promote neuronal degeneration during development.

—A strong negative correlation existed between levels of homocysteine and activity of the enzyme glutathione peroxidase (GPx) in the autistic children. "We expected this correlation to be negative," the researchers say, "because GPx synthesis is known to decrease with elevated levels of homocysteine." GPx plays a crucial role in protecting cells against oxidative damage, which previous research (see ARRI 19/2, 18/4) links to autism.

—Vitamin B12 levels were suboptimal in seven of the autistic children, and low for two others. The researchers say this could be due to poor absorption of B12 in the ileum, the region of the intestine containing receptors that pull B12 into the bloodstream. "Decreased B12 levels are expected to impair transmethylation of homocysteine to methionine," Pasca et al. say, "resulting in increased homocysteine levels and decreasing indispensable methylation reactions of proteins, phospholipids, DNA, and neurotransmitters."

—Autistic children showed reduced activity of PON1 arylesterase. PON1 is an antioxidant enzyme, and Pasca and colleagues say "decreased PON1 could explain the increased lipid peroxidation/oxidative stress observed… in autistic children and could be one of the steps leading to homocysteine toxicity in autism."

The researchers conclude, "Our study is the first one to indicate that hyperhomocysteinemia is present in children with autism and that high levels of homocysteine are negatively correlated with GPx activity and associated with low arylesterase PON1 activity and suboptimal B12 vitamin."

Editor's note: These findings are intriguing. DAN! researchers note, however, that only a minority of autistic children have elevated homocysteine—yet more evidence for the heterogeneity of the children labelled as "autistic."

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"High levels of homocysteine and low serum paraoxonase 1 arylesterase activity in children with autism," Sergiu Pasca, Bogdan Nemes, Laurian Vlase, Cristina E. Gagyi, Eleonora Dronca, Andrei C. Miu, and Maria Dronca, *Life Sciences*, November 16, 2005 (epub ahead of print publication). Address: Maria Dronca, Faculty of Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, CJ 400023, Romania, m_dronca@yahoo.com.