Biomedical Update:

R-THBP: Swedish study supports positive Japanese findings

Swedish researchers studying tetrahydrobiopterin (R-THBP) report that the substance may significantly benefit some autistic children. Their conclusions support earlier research by Japanese researchers (see ARRI 9/3, 4/2, 1 /4).

R-THBP is not a drug, but a natural enzyme that plays a role in the synthesis of serotonin and other neurotransmitters (brain "messenger" chemicals). In a three-month open trial, E. Fernell and colleagues administered the substance to six autistic children between three and five years of age. Only children with relatively low cerebrospinal fluid levels of R-THBP were accepted into the study.

"During the treatment period," Fernell et al. report, "all parents reported improvements in [children's] social functioning—mainly eye contact and desire to interact—and in the number of words or sounds which the [children] used." In addition, "small positive changes" were noted on developmental scales.

The researchers add that R-THBP levels in subjects' cerebrospinal fluid increased markedly after the therapy, and that PET studies revealed a change toward more normal levels of dopamine receptor binding in two brain areas, the caudate and the putamen.

Their study results, Fernell et al. say, suggest that R-THBP "might be useful for a subgroup of children with autism," but they caution that larger and lengthier double-blind studies are required.

In 1995, Yoshihiro Tani et al., who studied 20 autistic subjects and 10 non-disabled controls, found that cerebrospinal fluid levels of R-THBP and a related compound (NH2) were significantly lower in the autistic group than in the controls. The lowest levels were found in the youngest children studied.

Earlier, Hiroshi Naruse and colleagues administered R-THBP to 84 autistic subjects for 12 weeks, and reported that 53.7 percent of subjects receiving the substance showed significant improvement, compared to 30.9 percent taking the placebo. Naruse et al. found that R-THBP was most helpful for very young autistic children.

To ARRI's knowledge, R-THBP is not yet approved as an autism treatment in the United States.

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"Possible effects of tetrahydrobiopterin treatment in six children with autism—clinical and positron emission tomography data: a pilot study," E. Fernell, Y. Watanabe, I. Adolfsson, Y. Tani, M. Bergstrom, P. Hartvig, A. Lilja, A. L. von Knorring, C. Gillberg, and B. Langstrom; *Developmental Medicine and Child Neurology*, May 1997, Vol. 39, No. 5, pp. 313-318. Address: E. Fernell, Department of Paediatrics, Huddinge University Hospital, Sweden.

PET scans show serotonin abnormalities

A study by D. C. Chugani and colleagues offers new insight into the role of serotonin, a neurotransmitter, in autism.

About a third of all autistic children have increased blood platelet levels of serotonin. Measurements of serotonin byproducts in the cerebrospinal fluid of autistic subjects, however, have yielded inconsistent findings. Chugani and colleagues evaluated serotonin function in autism by a different method: they performed PET scans on eight autistic subjects, using tryptophan (a nutrient that is a building block of serotonin) as a tracer to directly study serotonin synthesis in the brain.

The researchers report that "asymmetries of serotonin synthesis were found in the frontal cortex, thalamus, and dentate nucleus of the cerebellum in all seven boys, but not in the one autistic girl studied." In addition, they say, "statistically significant differences between autistic boys and their non-autistic siblings were obtained" when comparing PET scans.

"These serotonergic abnormalities in a brain pathway important for language production and sensory integration may represent one mechanism underlying the pathophysiology of autism," the researchers say. Such abnormalities may also explain why drugs that affect serotonin levels in the brain can ameliorate some autistic symptoms.

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"Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys," D. C. Chugani, O. Muzik, R. Rothermel, M. Behen, P. Chakraborty, T. Mangner, E.A. da Silva, and H.T. Chugani; *Annals of Neurology*, Vol. 42, No. 4, October 1997, pp. 666-669. Address: D.C. Chugani, Department of Pediatrics, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, MI 48201.

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Surprising finding about chromosome 15 defect, autism

In recent years, researchers have reported on more than a dozen autistic children who have a "partial trisomy" of chromosome 15—that is, an extra copy of one specific section of the chromosome. New research by Edwin H. Cook, Jr., et al. indicates that this chromosome defect causes autism only when the defect is inherited from a child's mother, not the father.

Cook and colleagues studied a family with three children, two of whom were affected with autism. The children's mother, who was not disabled, had inherited the chromosome 15 defect from her father. Two of her children inherited the defect from her, and both were autistic; the third, who did not inherit the gene, was not disabled.

"Although our information comes from a single family," the researchers say, "it appears that paternally inherited duplications of [the chromosome region] 15q11-q13 lead to a normal phenotype"—that is, the absence of symptoms. In contrast, they theorize, "maternally inherited duplications usually lead to autism or atypical autism." This indicates, they say, that "an imprinted gene may contribute to susceptibility to autism in some cases." Imprinting is a phenomenon in which genes can differ slightly depending on whether they were inherited from the mother or father.

The researchers conclude that "careful examination of [this area on chromosome 15] is now indicated for cytogenetic studies of patients with autism or atypical autism."

This same area of chromosome 15 has been the object of intense study, because it is linked to two other genetic disorders that cause developmental disabilities—and these disorders also are linked to "imprinted" genes. Deletions of the 15q11-q13 chromosome area cause either Prader-Willi syndrome or Angelman ("happy puppet") syndrome, depending on whether the gene defect is inherited from the mother or the father.

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"Autism or atypical autism in maternally but not paternally derived proximal 15q duplication," Edwin H. Cook, Jr., Valerie Lindgren, Bennett L. Leventhal, Rachel Courchesne, Alan Lincoln, Cory Shulman, Catherine Lord, and Eric Courchesne; *American Journal of Human Genetics*, Vol. 60, No. 4, April 1, 1997, pp. 928-934. Address: Edwin H. Cook, Jr., Department of Psychiatry, MC 3077, 5841 South Maryland Avenue, Chicago, IL 60637.