The oxytocin/autism link: more questions than answers

A recent *Newsweek* article on the possible role of the brain chemical oxytocin in autism has raised interest—and questions.

In the May 13 issue, researcher Eric Hollander reported that when he administered oxytocin to five autistic individuals, they became more talkative and "twice as 'happy'." Hollander also tentatively linked the social phobias seen in autistic individuals to the use of pitocin (a synthetic form of oxytocin) during labor. "Most of the mothers of patients we see have had pitocin-induced labor," Hollander told *Newsweek*.

Hollander is not the first researcher to suggest a link between oxytocin and autism, but the nature of that link is unclear and the research seemingly is contradictory. Among the oxytocin/autism findings:

— Ryoko Hattori et al. compared the rates of autism in children born in different hospitals, and reported that children born in a hospital routinely using a combination of anesthetics including oxytocin had a significantly higher rate of autism than children born in three other hospitals which rarely used general anesthesia (see ARRI 5/3, 1991).

—Thomas Insel and Lawrence Shapiro, who studied mammals called voles, found that prairie voles, which are nurturing and social, had three times as many receptors for oxytocin in the prelimbic cortex of the brain, and seven times as many in the nucleus accumbens, as mountain voles—who avoid other voles except to mate, and abandon their infants (see ARRI 6/3, 1992).

—Charlotte Modahl et al., also investigating the role of oxytocin in sociability and nurturing behavior, concluded in 1992 that "there is a growing body of evidence that oxytocin promotes emotional attachment behavior across the wide spectrum of activities in which it is involved," and that "higher oxytocin blood levels have been correlated with stronger human mother-infant bonding and with more social and outgoing personalities in men and nonpregnant women." They suggest that magnesium and the drug naltrexone, both reported to increase sociability in some autistic children, may work because they increase levels of oxytocin or enhance its functioning (see ARRI 6/3, 1992).

—Jaak Panksepp, noting that oxytocin reduces vocal activity and alters pain sensitivity, argues that oxytocin levels may be too high, not too low, in autistic individuals. Panksepp is intrigued by research showing that oxytocin administration can produce stereotypical wing flapping in birds that resembles the arm flapping of many autistic children. (See ARRI 7/4, 1993.)

—James Leckman studied individuals with obsessive-compulsive disorder (OCD), and reported in the *Journal of the American Medical Association* in December 1994 that many of his subjects had strikingly elevated cerebrospinal fluid levels of oxytocin. The finding was true only for OCD patients with no personal or family histories of Tourette syndrome or other tic disorders.

Neurologist K. G. Woodward, in a letter to ARRI, notes that "the apparent improvement in language and sociability from oxytocin [in the Hollander report] contrasts with the suspicion that oxytocin given during labor and delivery causes or worsens autism." He adds that the link between high oxytocin and OCD symptoms "further complicates matters," since many autistic individuals exhibit symptoms of OCD—yet Hollander's subjects reportedly improved when given the hormone.

Woodward also notes, "It seems improbable that a single dose of oxytocin, an endogenous hormone naturally present during labor, would lead to cerebral maldevelopment," even when given during the critical neonatal period. "On the other hand," he speculates, "an indirect effect is certainly possible, as excessive oxytocin may cause forceful uterine contractions" and reduce the supply of blood to the fetal brain. But evidence from post mortem examination of the brains of autistic individuals suggests, he says, that autism is determined early during the course of fetal development, rather than at birth or afterward.

Does oxytocin given during labor contribute to autism? Can oxytocin given to autistic children reduce their symptoms? And do autistic children have too little, or too much oxytocin in their brains? The research is fascinating, but contradictory.

Hollander, on the other hand, theorizes that there is a genetic predisposition to shyness, obsessive-compulsive behaviors, and/or communication problems, but that this genetic predisposition does not manifest as autism unless brain damage occurs. "Without the brain damage," Hollander suggests in *Newsweek*, "you get a disorder marked by great social phobias, or else these 'odd' family members who have special skills such as being human calculators." But with brain damage, he says, "you get autism."

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"Life in a parallel world," Sharon Begley and Karen Springen; *Newsweek*, May 13, 1996.

—and—

"Oxytocin and autism," K. G. Woodward, personal communication to ARRI, July 1996.

—and—

"Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder: comparison with Tourette's syndrome and healthy controls," James F. Leckman; *Journal of the American Medical Assoc.*, Vol. 272, No. 22, December 14, 1994, p. 1718.

(See earlier issues of ARRI, noted above, for additional references.)

Update: drug treatments

Risperidone side effect

Preliminary research results suggest that the drug risperidone, commonly used to treat schizophrenia, can sometimes be more effective in reducing autistic symptoms than other neuroleptic drugs, and may have fewer side effects (see ARRI 10/2 and 8/4). But the drug is not free of risk, as one doctor recently noted in a letter to the *Journal of the American Medical Association*.

Daniel Tarsy reports that four days after being started on risperidone, one of his patients, a 43-year-old woman with schizophrenia, developed neuroleptic malignant syndrome. This disorder, potentially fatal, occurs when drugs that block dopamine receptors in the brain cause a disruption in the temperature-regulating mechanisms, leading the body to "overheat." Symptoms include fever, severe muscle rigidity, profuse sweating, rapid heartbeat and breathing, pallor, incontinence, delirium, stupor, and/or coma. Tarsy's patient suffered severe symptoms, but eventually recovered from the disorder.

"Neuroleptic malignant syndrome has recently been reported in a total of five [risperidone-using] patients from England, Finland, and the United States," Tarsy notes, saying that four recovered while the fifth died.

"Despite the reported safety of risperidone," he cautions, "continued vigilance for extrapyramidal toxicity remains appropriate during the use of any antipsychotic medication with dopamine-receptor blocking properties."

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"Risperidone and neuroleptic malignant syndrome," Daniel Tarsy, *Journal of the American Medical Association*, Vol. 275, No. 6, Feb. 14, 1996, p. 446.

Clozapine trial

In a letter to the *American Journal of Psychiatry*, Alessandro Zuddas et al. report that three autistic patients who had not responded to other drug treatments showed a positive response to clozapine. After three months of clozapine treatment, the researchers say, the children showed significantly less hyperactivity, fidgetiness, and aggression.

ARRI 10/1 summarized a report by Ron Hammock et al. regarding the successful use of clozapine to treat serious violence and self-injury in a patient who had not responded to behavioral therapies or other drugs.

Clozapine is likely to remain a "last resort" drug, however, because it can cause severe side effects including seizures and agranulocytosis, a serious and sometimes fatal blood disorder. In addition to clozapine's side effects, the drug and the monitoring required for patients taking it cost around $9,000 per year.

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"Clinical effects of clozapine on autistic disorder," Alessandro Zuddas, Maria Giuseppina Ledda, Annalisa Fratta, Pierandrea Muglia, and Carlo Cianchetti; *American Journal of Psychiatry*, Vol. 153, No. 5, May 1996, p. 738.

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