

Developmental Disorders and Dairy Products, Grains, Gluten and Other Proteins

By Margaret Lahey and Shari Rosen

BAMFORD-LAHEY CHILDREN'S FOUNDATION

VIII. DEVELOPMENTAL DISORDERS AND DAIRY PRODUCTS, GRAINS, GLUTEN AND OTHER PROTEINS

Another food category that has been associated with developmental disorders is protein. In this section, we first review how proteins could possibly be related to behavior or cognitive problems and then present the hypotheses and some evidence linking particular proteins with some developmental disorders.

VIII.a INTRODUCTION

Proteins consist of long chains of units referred to as amino acids. Digestive enzymes break down proteins into these long chains of amino acids. Incomplete digestion of protein leaves short chains of amino acids referred to as peptides. Such incomplete digestion is usually the result of enzymatic deficiency. A healthy intestinal wall does not allow macromolecules to pass; it bars un-degraded or partly degraded dietary proteins and most peptides are excreted in the urine. However, with increased intestinal permeability, some peptides can pass from the intestines into the blood stream where they may set up an immune reaction because they are considered foreign substances. Increased intestinal permeability can be identified by the presence of antibodies to peptides or by measuring sucrose permeability (e.g., Arnason, Gudjonsson, Freysdottir, et al., 1992; Catassi, Fabiani, Ratsch, et al., 1997; Smecuol, Bai, Vazquez, et al., 1997). Once in the blood stream peptides can also cross into the brain (Scott & Brandtzaeg, 1989).

Two sources of dietary protein (i.e., dairy products and grain) have been associated with adverse reactions not all of which involve allergen-specific immune response as measured by typical diagnostic techniques (e.g., Burks, Williams, Casteel, et al., 1990; Rasanen, Lehto, & Reunala, 1992). Some of the peptides associated with digestion of dietary proteins (e.g., milk, wheat) are in the opioid family (e.g., Fukudome & Yoshikawa, 1992; Ziodrou, Streaty, & Klee, 1979) and have psychoactive properties that can affect cognition and the release of neurotransmitters (Kampa, Loukas, Tsapis & Castanas, 2001). Opioids alter behavior because of their ability to bind to endorphin and enkephalin receptors in the brain. Endorphins and enkephalins are endogenous opioid-peptide neurotransmitters found in various parts of the brain and also produced by the pituitary gland. They are involved in the reduction of pain as well as in pleasure and reward (because they release dopamine). Animal research indicates that endogenous opioids also play a role in regulating both pre- and post-natal neural development (McLaughlin, Tobias, Lang, & Zagon, 1997; Zagon & McLaughlin, 1991). Endogenous opioids are also important in memory, learning, and behavior (e.g., Vaccarino & Kastin, 2001). Changes in endogenous opioid activity (e.g., by using opioid blockers) can induce food cravings and thus food intake (Mercer & Holder, 1997). Exorphins, such as opioids generated from digestion, attach to the same receptors as the endogenous opioids and can inhibit the breakdown of endogenous peptides and change the level of endogenous opioids (e.g., Mercer & Holder, 1997). Some suggest it is the opioid exorphins that are involved in the addictive behavior of some to the very foods that cause them problems (e.g., Brostoff, 1990). Therefore, concern about problems with digestion of dietary proteins involves allergic type reactions as well as the possible toxic effect of exorphins on behavior and learning.

VIII.b DAIRY

The proteins in cow's milk and associated byproducts (casein, beta lactoglobulin, alpha-lactoglobulin, bovine serum albumin, gamma-lactoglobulin) have been associated with adverse reactions particularly in children. For example, the estimated prevalence of intolerance to proteins in milk is from .5 to 7.5% in France (Olives & Breton, 1998) and cow's milk is the second most common allergy in children under two years-of-age in Spain (Pascual, Crespo, Perez, & Esteban, 2000). The protein casein that is found in cow's milk breaks down into casomorphine, which as implied in the name, has opioid properties. Evidence of antibodies to beta-casomorphin-8 has been found in the brain stem of infants suggesting that beta-casomorphins can be transported from the blood into the brain stem (Pasi, Mahler, Linsel et al., 1993). Two of the opioid peptides derived from milk (beta-casomorphin-7 and alpha-casein) have also been found to be histamine releasers in humans (Kurek, Czerwionka-Szaflarska, & Doroszewska, 1995; Kurek, Przybilla, Hermann, & Ring, 1992). Certain peptides that are derived from casein activate opioid receptors to respond and a couple of peptides function as antagonists to the activation of opioids receptors (Teschemacher & Koch, 1991; Teschemacher, Koch, & Brantl, 1997). Even breast fed infants can have problems related to cow's milk that has been ingested by the lactating mother (Wilson, Self & Hamburger, 1990). Interestingly, early exposure to cow's milk in preterm infants who have a family history of allergies increased their risk of developing a wide range of allergies, particularly manifested as eczema (Lucas, Brooke, Morley, et al., 1990). Whereas intolerance to milk protein has been associated with some developmental disorders, intolerance to proteins in grain have received the most attention; frequently reactions to both co-occur in the same individual.

VIII.c GRAINS

Cereal grain contains gluten (i.e., wheat, rye, oats, barley), which is a mixture of individual proteins including prolamines and glutelins. Gliadin is a prolamine that is found in wheat and is a major problem in celiac disease. But different grains have different prolamines and the kind and amount of prolamine influences the reaction an individual may experience, thus explaining the variability of reactions to these foods. Although it is not clear exactly how gluten causes problems of intolerance, symptoms of intolerance generally disappear with the elimination of all gluten from the diet. A diet free of gluten requires the elimination of most grains and grain products as well as other processed foods that contain small amounts of gluten. Grain also contains a number of opioid residues, which can be released during digestion (e.g., gliadinomorphine). The gluten exorphin A5 has been found to affect both the peripheral and central nervous system of mice (Takahashi, Fukunaga, Kaneto, et al., 2000).

Problems related to intolerance of gluten are often referred to as gluten enteropathy, non-tropical sprue, or celiac disease. Symptoms can include diarrhea, weight loss, anemia, and malnutrition related to malabsorption. In those suffering from long standing celiac disease, the mucosa of the small intestine is smooth with few villi; villi shed cells containing digestive enzymes and absorb food molecules. Intestinal permeability is common with celiac disease and decreases on a gluten free diet (Catassi, et al., 1997; Smecuol, et al., 1997; Vogelsang, Schwarzenhofer, & Oberhuber, 1998). Earlier estimates of the prevalence of confirmed celiac disease have ranged from 1:200 to 1:300 (Grodzinsky, Franzen, Hed & Strom, 1992; Horvath & Mehta, 2000; Not, Horvath, Hill, et al., 1998). However, some data suggest that the prevalence of gluten intolerance may be underestimated (Van Gossum, Mascart, Rickert et al., 2000). For example, a recent study estimated that the prevalence of celiac disease may be as great as 1:99 among children in Finland (Maki, Mustalahti, Kokkonen, et al., 2003). Most patients with established celiac disease have high IgM antibodies and IgA anti-gliadin antibodies (Arranz, Bode, Kingstone, & Ferguson, 1994). It appears, however, that some individuals whose tests show antibodies to gluten have few of the symptoms of celiac disease including no signs of mucosal damage (Arranz et al., 1994; Catassi, et al., 1997), whereas others

may have some symptoms such as irritable bowel syndrome (Wahnschaffe, Ulrich, Riechel, & Schulzke, 2001).

VIII.d DEVELOPMENTAL DISORDERS

Sensitivity to proteins and high intestinal permeability have been associated with a number of neurological and behavioral disorders in groups of adults and children (e.g., Pfeiffer, 1996). In a group of adults with neurological dysfunction of unknown cause, high readings of antigliadin antibodies were found in both those with confirmed celiac disease and those with normal bowel mucosa (Cooke & Smith, 1966; Hadjivassiliou, Gibson, Danies-Jones, et al., 1996; Luostarinen, Pirttila, & Collin, 1999). In adults with epilepsy and with psychological problems such as depression, celiac disease also appears to be frequent (Corvaglia, Catamo, Pepe, et al., 1999; Cronin, Jackson, Feighery, et al., 1998; Gobbi, Boquet, Greco, et al., 1992).

Positive IgG antigliadin antibodies but no negative IgA antibodies were found in 13% of a group of children who had neurological dysfunction of various types (e.g., ADD, Migraine, epilepsy, motor abnormalities) leading the authors to conclude that there was little association between celiac disease and neurological problems in children (Lahat, Broide, Leshem et al., 2000). However, others disagree and provide evidence of such a relationship. For example, brain white-matter lesions was found in 20% of children with celiac disease (Kieslich, Errazuriz, Posselt, et al., 2001) and a higher prevalence than expected (14%) of confirmed celiac disease was found in a population of children with neurological disorders such as epilepsy, Down's syndrome, or slow psychomotor development (Salur, Uibo, Talvik, et al., 2000). Moreover, intestinal permeability has been associated with psychiatric disorders in adults with schizophrenia (e.g., Dohan, 1988; Singh & Kay, 1976; Wood, Hamilton, Axon, et al., 1987) and in children with autism (D'Eufemia, et al., 1996).

Down Syndrome. Not only has a higher than expected prevalence of celiac, or celiac-like, disease been found in children with Down syndrome (e.g., Reading, 1984; Salur, et al., 2000) but an increased incidence of Down syndrome, relative to the general population, has been reported among patients with celiac disease (Dias & Walker-Smith, 1990). The finding that those with Down syndrome who had celiac disease tended to have younger mothers than typically associated with Down syndrome led Dias and Walker-Smith (1998) to suggest a link between the two problems. Some reports indicate that the prevalence of confirmed celiac disease among Down's syndrome patients is from 2 to 7 percent (Carnicer, Farre, Varea, et al., 2001; Gale, Wimalaratna, Brotodiharjo, & Duggean, 1997); others suggest that the frequency of celiac disease among Down syndrome children may be 43 times greater than the general population of children (Hilhorst, Brink, Wauters, & Houwen, 1993). Moreover, increased levels of IgG and IgA relative to gliadin and gluten as well as high levels of urine peptide are found among many individuals with Down syndrome who do not have confirmed Celiac disease (Nygaard, Reichelt, & Fagan, 2001; Reichelt, Lindback, & Scott, 1994; Storm, 1990). Most relevant is the finding of a significant negative correlation between levels of antibodies to gliaden and gluten and levels of psychological functioning (Nygaard, et al., 2001). Although the association between Down syndrome and reactions to certain proteins is well documented, we did not find any data on dietary intervention with Down syndrome. One paper reported on a group of parents who felt their children had food allergies and tried an elimination diet; 66 percent reported beneficial effects but results were not reported by type of food (Bade, Rammeloo, Hermans, et al., 1995).

Autism. The etiology of autism is uncertain and might vary among individuals (e.g., Gilberg, Trygstad, & Foss, 1982; Trottier, Srivastava, & Walker, 1999). Hypotheses regarding etiology include genetics, environmental toxins, infectious agents, enzymatic problems, and dietary factors. In this section we discuss some evidence related to the hypothesis that digestive and dietary factors may be involved. Particular interest has been directed to the relation between childhood autism, as well as schizophrenia, to problems with the proteins that occur in dairy and grain products (Dohan, 1983; Horvath, et al., 1999). Such problems involve immune responses as well as gastrointestinal

symptoms. For example, researchers at the University of Minnesota have found T-cell reactivity to the dietary proteins in soy, milk, and wheat in 75 to 80% of a group of 83 children with autism (Reuters Medical News, 2001b). Others have related problems with dietary proteins to the gastrointestinal symptoms frequently found among these populations (e.g., Goodwin, Cowen, & Goodwin, 1971; Hovrath, et al., 1999; Wakefield, et. al., 1998; Quigley & Hurley, 2000).

One explanation for the relation between gut and brain problems is intestinal permeability. Intestinal permeability can allow passage of the opioid peptides from food proteins such as gluteins and caseins to pass into the blood stream and enter the brain. Some hypothesize that the behaviors seen in autism and schizophrenia could be the result of exogenous peptides affecting neurotransmission and the neuro-regulatory role normally performed by the endogenous opioid peptides such as enkephalins and endorphins (e.g., Dohan, 1988; Singh & Kay, 1976; D'Eufemia, et al., 1996; Mehl-Madrona, 2000; Shattock & Savery, 1996). An argument in support of this hypothesis, often referred to as the opioid excess hypothesis, is that some symptoms of autism (e.g., diminished sensitivity to pain, limited clinging behavior, unpredictable response to stimuli, reduced socialization, repetitive stereotyped behavior) can be simulated in animals by administering opiates during infancy (Panksepp, 1979, as cited by Deutsch, 1986; Sher, 1997). Moreover, when gluten exorphin, a fragment from wheat gluten, was injected into mice it suppressed pain-inhibition and influenced emotionality and memory processes affecting both peripheral and central nervous system (Takahashi, et al., 2000). These are all, of course, symptoms found in autism. Moreover, unique urinary peptide patterns have been found among autistic children as compared with those of normally developing peers and children who have mental retardation without psychoses (Gilberg, et al., 1982; Reichelt, Hole, Hamberger, et al., 1981). Some suggest that many of the peptides found in the urine are derived from the incomplete breakdown of food and that they may well result in enhanced opioid activity (Shattock & Savery, 1996).

The opioid excess hypothesis has also been tested by examining the effect of various treatments on the behavior of children with autism including the use of opiate antagonists and the dietary exclusion of gluten and caseins. Level of beta-endorphin has been correlated with severity of stereotypic behavior in children with autism (Ernst, Devi, Silva et. al., 1993). Naltroxone is a specific opiate antagonist that blocks the action of endogenous opioids at opiate receptors and is an approved treatment for substance abuse such as heroin addiction. It has been reported to have positive effects in schizophrenia and on impulse control in animals (Deutsch, 1986; Soderpalm & Svensson, 1999). A number of studies have examined its effect on children with autism. Some case studies and small clinical trials have reported that a some autistic children treated with naltroxone show significant reduction of symptoms including hyperactivity, self-injurious behavior, aggressiveness, poor attention, inappropriate social and play behavior with no improvement in learning skills (e.g., Bouvard, Leboyer, Launay, et al., 1995; Campbell, Anderson, Small, et al., 1993; Cazzullo, Musetti, Musetti, et al., 1999; Kolmen, Feldman, Handen & Janosky, 1997; Leboyer, Bouvard, Launay, et al., 1993; Scifo, Cioni, Nicolosi, et al., 1996; White & Schultz, 2000). In contrast to these findings, other studies report little effect of naltroxone on maladaptive and social behavior including communication skills (e.g., Feldman, Kolmen, & Gonzaga, 1999; Willemsen-Swinkels, Buitelaar, & van Engeland, 1996; Willemsen-Swinkels, et al., 1995; Zingarelli, Ellman, & Hom, 1992). These data could be interpreted as weak evidence in support of the opioid excess theory.

Studies on dietary intervention come mainly from Europe, primarily Norway and Great Britain. Some success with removal of gluten and casein from the diet has been reported for patients with schizophrenia (e.g., De Santis, Addolorato, Romito, et al., 1997; Singh, & Kay, 1976). In fact, Dohan and colleagues point out that schizophrenia is rare in cultures where grain is rare in the diet (Dohan, Harper, Clark et al., 1984). Dietary changes suggested for children with autism are most often reduction or removal of casein and/or gluten. Parents of children with autism have reported that such dietary intervention had a significant impact on their child's behavior (Shattock, 1995). In a summary of seven group studies, plus three case studies and two surveys on dietary intervention with autistic children, Knivsber, Reichelt and Nodland (2001) report positive changes in autistic

behavior in all but one study, as well as a reduction in number of epileptic fits and changes in urinary peptide abnormalities in all studies that considered these latter two factors. For example, in a case study of an 8-year-old boy with autism, investigators found that certain foods (such as wheat, corn, sugar and dairy products) produced behavior disorders (O'Banion, Armstrong, Cummings, & Strange, 1978). One study found that autistic patients had higher levels of antibodies to casein than controls and that an 8-week period of a diet free of cow's milk yielded marked improvement in symptoms (Lucarelli, Frediani, Zingoni, et al., 1995). Some researchers report dietary intervention with autistic children brought about improvement in the urinary peptide pattern as well as in educational and developmental measures (Knivsberg, Reichelt, Høien, & Nodland, 2002; Knivsberg, Wiig, Lind, et al., 1990). In contrast, others found no change in urinary profile, although they also reported improvement on a number of behavioral measures (Whiteley, Rodgers, Savery, & Shattock, 1999). At the 12th International Conference on Autism, Kniker reported that elimination of dairy, grains, food additives, and caffeine dramatically changed behavior of about one-third of the autistic children observed, however, half of these children improved whereas half deteriorated (Reuters Medical News, 2001b). Finally, one study reported no association between ingestion of gluten and symptoms of autism and concluded that gluten-free diet could be just another way to isolate the individuals in this group (Sponheim, 1991). Thus, results are mixed but some preliminary evidence supports Hypothesis D, that dietary intervention involving removal of casein and gluten may help a few children with autism. Unfortunately, many of the studies reporting on dietary intervention are difficult to obtain through the usual sources (e.g., PubMed) and many are not reported in peer-reviewed journals. Clearly more research is needed to clarify whether the opioid excess theory can be supported and if changes in diet are the most appropriate intervention.

Source: <http://www.childrensdisabilities.info/allergies/developmentaldisordersprotein7.html>