11

GUT EOSINOPHILIC INFILTRATION IS ASSOCIATED WITH INCREASED INTESTINAL PERMEABILITY IN COW'S MILK FED SUCKLING RATS.

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The postnatal cessation of enhanced intestinal permeability in rats is controlled by activation of mucosal immune system. To study the effects of early antigen exposure on this process, rat pups were divided in three groups from 14 until 21 d of age. Controls (n=8) remained on normal maternal milk. In addition to this, group CM (n=8) received daily a gavage feed of cow's milk, in group D (n=6) cow's milk was given to dams. From HE stained oriented jejunal sections, mucosal eosinophils were counted on the basis of morphology using 400 x magnification, total area being 1.0 mm^2 including epithelium and lamina propria. Intestinal absorption of horseradish peroxidase (HRP) was assessed in vitro in Ussing chambers. The number of eosinophils, mean (95 % CI)/mm^2, was significantly higher in group CM; 303 (275, 331), than in group D; 162 (105, 219), and in controls; 185 (154, 216), p=0.0001. In the same way, the absorption of intact HRP, geom. mean (95 % CI) ng x h^{-1} x cm^{-2}, in group CM; 50 (35, 71), exceeded that of group D; 27 (17, 43), and controls; 11 (8, 16), p=0.0001. The absorption of degraded HRP was comparable in all groups. Our results show that foreign dietary proteins enhance intestinal permeability. The presence of eosinophils suggests that this is caused by an immune-mediated tissue dysfunction. Eosinophils, by releasing inflammatory mediators, may be important elements in such local hypersensitivity reactions.

12

EFFICIENT ANTIGEN SPECIFIC IMMUNE ELIMINATION IN THE GUT IS A PREREQUISITE FOR CLINICAL FOOD TOLERANCE.

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To obtain evidence on local immune responses to dietary antigens in health (H) and in cow milk allergy (CMA), the ELISPOT assay of immunoglobulin (ISC) and specific antibody (sASC) secreting cells among blood lymphocytes was used. It reflects indirectly immunological events in the gut. Twenty healthy infants (mean age 5 mo) and 18 infants with CMA (7.5 mo) were studied. The numbers of ISC were lower in CMA than in H infants:

	ISC (mean[95% confidence interval]/10^6 cells)		
	IgA	IgM	IgG
H	917[584,1439]	1228[726,2078]	1438[834,1503]
CMA	172[19,1577]	180[38,853]	385[74,2016]

sASCs of the IgA isotype against ß-lactoglobulin were found in 12/20 and against casein in 10/20 H infants, but in only 2/18 and 1/18 CMA infants. The response to clinical milk challenge in CMA: strong antigen nonspecific (ISC), small and inconsistent sASC.

We conclude that a focused immune defense at the mucosal level is crucial in acquiring clinical tolerance to food antigens.

13

SUPPRESSOR CELL ACTIVITY AND INTERFERON-GAMMA (IFN-GAMMA) PRODUCTION ARE DEFECTIVE IN COW'S MILK ALLERGY (CMA)

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The pathogenetic mechanisms of CMA are unknown. To elucidate the function of immunoregulatory lymphocytes in this disorder, activity of non-specific and cow's milk-induced suppressor cells was studied and their capacity to generate IFN-gamma was evaluated. The study comprised 28 infants, aged from 2.6 to 60.0 months, who had CMA manifested with skin (n=8) or gastrointestinal (n=6) symptoms, or were studied as controls. Isolated lymphocytes were induced by Con A or cow's milk and their ability to suppress the T-cell proliferative response of a healthy person was studied by co-culture. The IFN-gamma production was evaluated by ELISA from culture supernatants.The Table illustrates the mean [95% CI] suppression and antigen-induced IFN-gamma production in study patients.

GROUP	SUPPRESSION (%)		IFN-GAMMA PRODUCTION (pg/ml)	
	Con A	Cow's milk	Con A	Cow's milk
CMA	7 [1, 12]	2 [-6, 10]	0	0
CONTROLS	19 [14, 24]	26 [14, 33]	17 [12, 31]	12 [9, 17]

The suppression induced by Con A or cow's milk was significantly lower in patients who had CMA, when compared with that of controls; F=13.1, p=0.0001 and F=10.4, p=0.0001, respectively. Lack of suppression was comparable in CMA patients with skin or gastrointestinal symptoms. The generation of IFN-gamma was absent in CMA indicating insufficiency in T-cell function. We conclude that lack of normal suppression may be caused by delayed maturation of suppressor cell function in CMA. This defect may further lead to a disturbance in the control of T-cell activation. These novel findings may explain the natural history of this disease.

14

THE DIAGNOSTIC SIGNIFICANCE OF IGG-COW'S MILK ANTIBODIES-REEVALUATED.

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To determine the degree of sensitization against cow's milk(CM) we investigated IgG-antibodies(ab) against CM proteins in a prospective study of differently fed infants assigned to 6 feeding groups.

(Br)Breastfed exclusively (at least 4 weeks)(n=166);(Br+HA1)breast-fed,but initial supplement with a partly hydrolyzed whey/casein milk (n=66);(Br+HA2)breastfed,initial supplement with a highly hydrolyzed soy/collagen product(n=28);(Br+CM)breastfed,initial supplement with CM(n=58);(CM)only CM-formula(n=139);(HA2)fed with a highly hydrolyzed product for 2 months,followed by CM(n=45). CM-ab were determined by an indirect immunofluorescent test using a geometrical mean titer (gmt)for interpretation (Bürgin-Wolff,EJP 1980).Serum was taken during weaning 4 weeks after addition of CM or in the 4th month(groups CM,HA2) and in the 2nd year.(all groups).

In the 1st year of life the lowest gmt values were obtained in the groups(Br),(Br+HA1)and(Br+HA2),the highest in group(CM)and(Br+CM) without differences between atopic and non-atopic infants.In the 2nd year of life all values decreased except those in group(Br+HA1).Weaning after 3 months results in low gmt titers,whereas earlier weaning showed the highest titers in group(Br+CM)followed by(Br+HA1),(Br+HA2) and (Br).If all results were plotted against the ages there was much overlap between symptomatic and asymptomatic infants.Only the few CM-fed,very young infants with chronic gastrointestinal(GI) CM-protein intolerance(CMPI) showed very high titers,which helped to confirm the diagnosis.All had a relapse during a CM-challenge.The diagnostic significance of IgG-CM-ab is limited to infants with chronic GI CMPI.

BRAIN AND DEVELOPMENT

15

ARE SOMATOSENSORY EVOKED POTENTIALS PROLONGED IN THE FIRST 24 HOURS OF LIFE?

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Recently it has been suggested that the N1 peak latency is different in normal neonates studied during the first postnatal day. It has been found to be abnormally prolonged but this difference is not found in those who received prenatal steroids. (1)

We have looked at N1 latency in 18 normal metabolically stable infants during the first 24 hours of life, gestation 29 - 40 weeks, birthweight 776-3830grams. 1 infant received prenatal steroids.

In all cases the N1 latency fell within our normal range (+/-2SD). When the N1 latencies were converted to standard deviation scores (SDS) the range was -1.83 to 1.53 SDS, median 0.04.

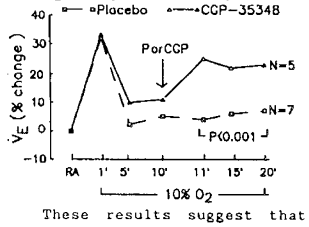
In conclusion we have been unable to demonstrate prolonged N1 latencies during the first 24 hours of life in neonates who are metabolically stable and suggest that SEPs are a useful marker of cerebral function during this time. Reports of transient abnormality may be due to technical differences.

(1) Pierrat V Et al, Somatosensory evoked potentials and adaptation to extrauterine life. Brain Dev 1990;12:376-9.

16

EFFECTS OF A GABA$_B$ RECEPTOR BLOCKER (CGP-35348) ON THE VENTILATORY RESPONSE TO HYPOXIA IN NEWBORN PIGLETS. Jian Huang, Cleide Suguihara, Jing Lin, Amed Soliz, Dorothy Hehre, and Eduardo Bancalari. Department of Pediatrics, University of Miami, Miami, Florida.

It has been postulated that increased CNS GABA levels may play an important role in the decrease in minute ventilation observed during sustained hypoxia in the newborn. In order to determine whether the changes in ventilation during hypoxia are mediated by GABA$_B$ receptors, 12 sedated, spontaneously breathing newborn piglets (age, 5±1 d; wt, 1678±473 g) were studied. Minute ventilation (V_E), arterial blood pressure (ABP) and arterial blood gases were measured in room air (RA) and at 1, 5 and 10 min of hypoxia (FiO_2=0.10) before drug intervention. All measurements were repeated after an infusion of placebo (P) or the GABA$_B$ receptor blocker, CGP-35348 (100-300 mg/kg, IV) while the animals remained in hypoxia. CGP-35348 crosses the blood-brain barrier and is a potent and specific GABA$_B$ receptor blocker. Basal V_E was similar in both groups. During hypoxia V_E increased significantly only in the animals who received the GABA$_B$ antagonist. Changes in PaO_2 and ABP were similar between groups before and after P or GABA$_B$ antagonist infusion.



These results suggest that the depression of the ventilatory response to sustained hypoxia in the neonate is in part mediated by increased CNS GABA acting through GABA$_B$ receptors.