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The Effects of Dietary Nucleotides on Intestinal Blood Flow in Preterm Infants

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ABSTRACT

Nucleotides (NT) are reported to affect development of the immune and gastrointestinal systems, and they are currently added to most term infant formulas. In the present study, dietary NT effects on superior mesenteric artery blood flow were investigated. Formula-fed preterm infants were studied once with a 20 kcal/oz. term infant formula containing 80.6 mg/L of NT (NT+), and once with the same formula with no added NT (NT−) (n = 20, gestational age 28.0 ± 2.2 wk). A reference group of preterm infants fed human milk was also studied (n = 20, gestational age 29.0 ± 1.6 wk). Superior mesenteric artery blood flow velocities (BFV) were measured by Doppler ultrasound 15 min before and 30, 60, and 90 min after the start of the feed. BFV rose in all infants from baseline to 30 min after feed initiation, and progressively declined thereafter in infants fed NT− or human milk. However, NT+ feedings were associated with a minimal change in BFV between 60 and 90 min. As a result, the difference in blood flow velocities between baseline and 90 min was significantly greater with the NT+ *versus* the NT− feedings for the mean, peak systolic, and end diastolic velocities (p = 0.03, 0.05, and 0.03, respectively). BFV after the NT− and human milk feedings were similar. These data suggest that orally administered NT are associated with effects on the intestinal vasculature. **(*Pediatr Res* 52: 425–429, 2002)**

Abbreviations

SMA, superior mesenteric artery
BFV, blood flow velocity
NT, nucleotide
NT+, formula with added nucleotide
NT−, formula with no added nucleotides

The splanchnic circulation accounts for 20% of cardiac output, and at times it may contain one-third of the blood volume (1, 2). The inferior portion of the duodenum, the whole of the small bowel, and the right half of the colon are supplied by the SMA. The dependence of intestinal blood flow on a single vessel implies that changes in SMA blood flow patterns may have significant physiologic effects on the bowel (3, 4).

The transcutaneous Doppler flow method has been used to evaluate intestinal circulation in infants. Factors including postnatal age, gestational age and birth weight (5–13), intrauterine growth restriction (6, 14–16), birth asphyxia (17), various pharmacologic agents (18–22), and phototherapy (23, 24) are reported to affect splanchnic blood flow patterns in infants.

SMA BFV increases after enteral feeding. Factors that reportedly affect postprandial SMA BFV in infants include feed volume (5, 13), interval (24), and composition (3, 8, 24–26). We (27) and others (28) have reported that increases in SMA BFV were greater in term infants after a feeding of formula with added NT compared with the same formula with no added NT. NT are naturally occurring substances in human milk, and studies in animals and human infants suggest they influence the development of the immune and gastrointestinal systems (29–32). We investigated the effects of feeding NT supplemented formula on SMA BFV in preterm infants.

METHODS

This protocol was approved by the Institutional Review Board for the Protection of Human Subjects at the University of South Florida. Informed consent was obtained from the parents of each enrolled infant.

Subjects. Inclusion criteria were gestational age <31 wk, birth weight <1800 g, and appropriate for gestational age. Infants with evidence of a patent ductus arteriosus or other cardiac abnormality, evidence of a gastrointestinal abnormal-

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Table 1. *NT content of the study formulas (mg/L)*

	NT−	NT+
Total Nucleotides	7.5	80.6
CMP	3.1	38.8
UMP	3.5	16.6
AMP	0.4	12.0
GMP	0.5	13.2

NT present in NT− are inherent to milk ingredients, whereas NT+ was supplemented with approximately 72 mg/L NT. CMP, cytidine monophosphate; UMP, uridine monophosphate.

ity, ventilatory requirement at the time of study, and phototherapy within 6 d of being studied were excluded. Infants for whom complete measurements could not be made due to the presence of abdominal gas were excluded. Formula-fed and human milk-fed infants had received more than 90% of their total enteral intake as formula or human milk, respectively, before the studies.

Feedings. Study feedings for formula-fed infants were a 20 kcal/oz. ready-to-feed term infant formula with the same composition as Similac with Iron (NT+), or the identical formula with no added NT (NT−). The NT content of the NT+ formula, 80.6 mg/L, was similar to that reported for human milk (33) (Table 1). The formulas were identified by a code, and the investigators were blinded to formula identities until all studies were completed and data were analyzed. Study feedings for human milk-fed infants were their mothers' own, previously frozen, unfortified breast milk.

Study design. Infants were fed at 3-h intervals, and were studied once their enteral intakes were >200 mL/kg/d. Each formula-fed infant served as his or her own control, and was studied using a cross-over design as follows: infants were randomized to be studied with a feeding of NT+ on study d 1 and with NT− on study d 2 (group 1, $n = 10$), or with a feeding of NT− on study d 1 and a feeding of NT+ on study d 2 (group 2, $n = 10$). Study d 1 and 2 were consecutive days. Human-fed infants were studied with a single feeding of breast milk ($n = 20$).

Study feedings were given at the time of a regularly scheduled feeding between 1200 and 1500 h, 2 h and 45 min after the previous feeding was started. All study feedings were administered at 30 mL/kg, and were delivered by gravity *via* a nasogastric tube.

Ultrasound measurements. An Interspec Apogee CX annular phased color system with a 7.5-MHz Doppler probe (ATL, Inc., Bothell, WA, U.S.A.) was used to measure time-averaged mean, peak systolic, and end diastolic SMA BFV 15 min before the start of the study feed (baseline), and 30, 60, and 90 min later. For imaging, the transducer was placed on the mid abdomen above the umbilicus in the sagittal plane. Color flow mapping was used to identify the SMA where it originated from the aorta. The sample volume of the pulsed Doppler was placed a few millimeters distal to the origin of SMA, using an angle correction of 25°. Blood pressure, heart rate, and respiratory rate were recorded at baseline, and the hematocrit was noted. All Doppler studies were performed by one of two ultrasound technicians, however, one technician performed all measurements on a given day.

Statistical analyses. A cross-over statistical design was used to compare diet effects on SMA BFV measurements between group 1 and group 2 infants as follows: the change in velocity from baseline to 30, 60, and 90 min was calculated for study d 1 and 2. The study d 1 changes in velocity were subtracted from the study d 2 changes in velocity; these calculated differences were compared between group 1 and group 2 using a *t* test.

Comparisons between the combined formula-fed groups and the reference human milk-fed group for baseline BFV and changes in BFV after feedings were analyzed using a three-way ANOVA.

RESULTS

Birth weight, gestational age, day of life at the time of study, gestation-corrected age, and weight at the time of the study were similar between groups 1 and 2 (Table 2). Postnatal age at the time of the studies was lower for the reference group of human milk-fed infants, reflecting better feed tolerance and more liberal advancement of enteral feedings for human milk-fed infants. Between study groups there were no differences in blood pressure, heart rate, respiratory rate, hematocrit, or time required to deliver the study feeding volume *via* the nasogastric tube.

There were no significant differences in baseline BFV between groups 1 and 2 on study d 1 and 2. The cross-over statistical analysis revealed that the difference in BFV between baseline and 90 min was significantly greater with the NT+ *versus* the NT− feedings for the mean, peak systolic, and end diastolic velocities ($p = 0.03, 0.05, 0.03$, respectively, Table 3).

Table 2. *Characteristics of study infants*

	Formula fed		Human milk fed
	Group 1: NT+ ⇒ NT− ($n = 10$)	Group 2: NT− ⇒ NT+ ($n = 10$)	Reference ($n = 20$)
Birth weight (kg)	1.2 ± 0.4	1.0 ± 0.4	1.3 ± 0.26
Gestational age (wk)	28.6 ± 2.2	27.4 ± 2.1	29.0 ± 1.6
Postnatal age (d) at time of study	41.0 ± 25.3	43.5 ± 20.8	26.7 ± 17.1
Gestation-corrected age (wk) at time of study	34.4 ± 2.6	33.6 ± 1.9	33.1 ± 2.0
Weight (kg) at time of study	1.6 ± 0.2	1.5 ± 0.3	1.5 ± 0.3

There were no significant differences between group 1 and 2 infants. Data are expressed as the mean ± SD.

Table 3. *Results of cross-over statistical analysis*

		Group 1: NT+ ⇒ NT− (n = 10)			Group 2: NT− ⇒ NT+ (n = 10)			
	Human milk (n = 10)	Day 1 NT+	Day 2 NT−	Day 1–Day 2 (X)	Day 1 NT−	Day 2 NT+	Day 1–Day 2 (Y)	p X *vs* Y
Mean								
−15 to 30 min	18.2 ± 2.9	21.3 ± 3.5	21.2 ± 3.4	0.1 ± 4.3	17.4 ± 6.7	27.3 ± 7.1	−9.9 ± 4.5	0.12
−15 to 60 min	12.1 ± 2.3	14.4 ± 3.0	10.8 ± 5.3	3.6 ± 5.9	17.2 ± 6.6	14.9 ± 3.4	2.3 ± 6.2	0.89
−15 to 90 min	4.8 ± 1.8	15.1 ± 6.0	1.2 ± 3.9	13.9 ± 8.6	8.4 ± 4.6	16.1 ± 4.5	−7.7 ± 2.7	0.03
Peak systolic								
−15 to 30 min	39.4 ± 6.6	45.9 ± 7.6	44.7 ± 5.7	1.2 ± 7.7	34.9 ± 13.2	54.5 ± 12.5	−19.6 ± 8.4	0.09
−15 to 60 min	26.1 ± 5.2	33.7 ± 6.4	25.9 ± 10.4	7.8 ± 11.7	30.4 ± 13.0	42.5 ± 7.2	−12.1 ± 10.8	0.23
−15 to 90 min	16.5 ± 5.0	40.1 ± 10.0	14.2 ± 8.6	25.9 ± 20.6	13.3 ± 7.2	33.1 ± 7.2	−19.8 ± 9.1	0.05
End diastolic								
−15 to 30 min	5.8 ± 1.4	6.8 ± 2.1	3.8 ± 1.6	3.0 ± 2.8	7.5 ± 2.4	6.2 ± 1.8	1.3 ± 3.0	0.69
−15 to 60 min	3.6 ± 1.3	1.9 ± 1.6	0.9 ± 2.0	1.9 ± 2.7	3.9 ± 1.7	2.9 ± 1.7	1.0 ± 2.3	0.80
−15 to 90 min	1.0 ± 0.9	2.3 ± 1.9	−2.1 ± 1.5	4.4 ± 2.4	0.6 ± 1.6	3.7 ± 2.0	−3.1 ± 2.2	0.03

Group 1 infants received NT+ on d 1, and NT− on d 2. Group 2 infants received NT− on d 1 and NT+ on d 2. The change in velocity (cm/s) for mean, peak systolic, and end diastolic velocities were measured from baseline (−15 min) to 30, 60, and 90 min after the start of a feed. The d 1 change in velocity was subtracted from the d 2 change in velocity for both groups (x and y for groups 1 and 2, respectively). A t test was used to measure the difference between x and y. Values for the reference group of infants fed human milk are also provided. Data are expressed as the mean ± SEM.

Figure 1 represents mean values after feedings with NT+, NT−, and human milk. The highest postprandial BFV for all infants was at 30 min. BFV declined from 30 to 90 min after feedings of NT− or human milk. However, after feedings of NT+ there was minimal change in BFV from 60 to 90 min. The three-way ANOVA revealed no significant differences among the human milk, NT−, or NT+ groups in baseline BFV or changes in BFV to 30 and 60 min. However, the change in BFV to 90 min was significantly greater after a feeding of NT+ compared with NT− and human milk for the mean (p = 0.015) and peak systolic (p = 0.033) velocities (data not shown).

Postprandial vascular resistance did not decrease among the three diet groups, which may be due to a lower than optimum sampling volume, and/or a high degree of variability in end diastolic velocities relative to peak systolic velocities.

DISCUSSION

Intestinal blood flow is regulated by intrinsic and extrinsic mechanisms as well as circulating vasoactive substances (1, 2, 34). The gastrointestinal tract is the source of a number of neurotransmitters, peptides, and autacoids, and its vascular supply is richly innervated by sympathetic and parasympathetic nerves (2). The mechanisms that regulate postprandial splanchnic vascular responses in infants, particularly those born prematurely, are unclear. Larger feed volumes (5) and longer intervals between feeds (25) are reported to result in higher relative postprandial SMA BFV, whereas smaller amplitude and longer latency in SMA BFV responses are reported after a feed with human milk *versus* formula (8, 25). In the present study, SMA BFV rose in all infants from baseline to 30 min after feed initiation, and began to decline thereafter. However, NT+ feedings were associated with a sustained increase in postprandial BFV to 90 min after feed initiation. These results are in agreement with studies in term infants (27, 28) demonstrating higher postprandial SMA BFV 90 min after a feeding with formula containing added NT compared with formula with no added NT or human milk.

The clinical significance of a sustained increase in postprandial SMA BFV is unknown. Fang *et al.* (35) reported a positive correlation between feed tolerance in preterm infants and postprandial SMA BFV 60 min after a feed, suggesting that higher postprandial BFV may be associated with a beneficial physiologic response. In the present study, postprandial BFV were higher after NT+ feedings. However, responses after NT− feedings were similar to those after human milk feedings, which are associated with better feed tolerance and clinical outcomes. The divergent SMA BFV response between infants fed human milk and those fed NT+ may relate to differences in NT composition; about 50% of the NT in human milk are present as RNA, NT+ formula was supplemented with the monophosphate form only (33). However, this is speculative given the numerous compositional differences between formulas and human milk.

The higher SMA BFV measured after NT+ feedings may reflect dilation of the intestinal vascular bed. AMP, one of the NT added to the NT+ formula, is hydrolyzed to adenosine within the intestinal lumen (36). Adenosine, a potent vasodilator, plays a role in the regulation of postprandial and reactive hyperemia (37–40). Studies in animals have demonstrated that infusion of adenosine into the arterial supply of the small intestine increases blood flow to the intestinal wall (37, 38, 41–43) and mucosal layer (44), particularly in younger animals (45, 46). In addition, luminal infusion of a NT mixture containing AMP was associated with intestinal hyperemia in newborn swine (46). The results of the present study further suggest that exogenous nucleotides can affect intestinal blood flow. However, in the present study and that of Özkan *et al.* (28), the most significant difference in BFV between formula feedings with and without NT was seen 90 min after initiation of the feed. Although the metabolic fate of formula NT is unknown, they are probably rapidly degraded within the intestinal lumen. Investigations in animals suggest that nucleosides are the primary form absorbed (47–49), and that over 90% of nucleosides, and purine and pyrimidine bases are absorbed into the enterocyte (50, 51). Once absorbed, most of the nucleosides

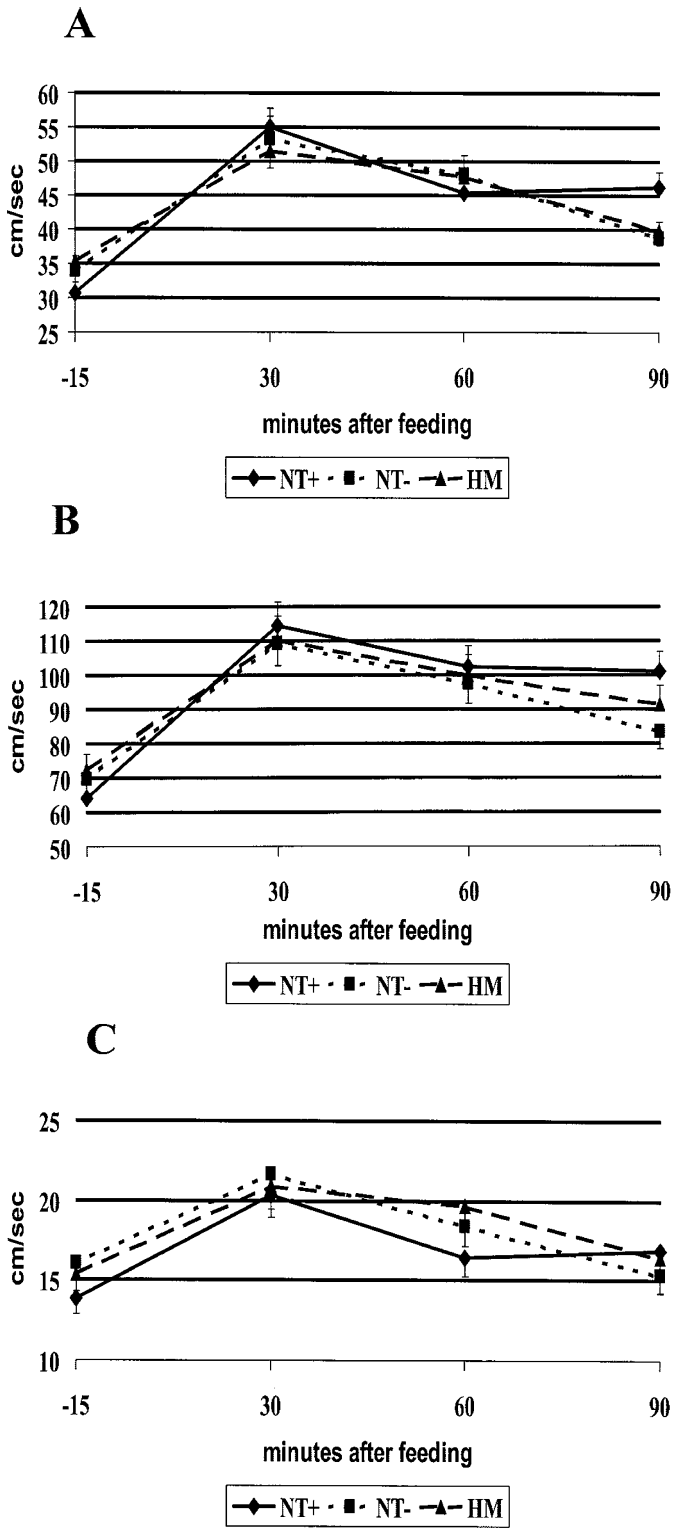

Figure 1. Mean velocity (*A*), peak systolic velocity (*B*), and end diastolic (*C*) velocities of blood flow in the superior mesenteric artery of preterm infants 15 min before and 30, 60, and 90 min after a feeding of NT+ or NT− formula, or with the infant's own mother's milk (*HM*).

and bases are rapidly degraded, and catabolic products are excreted in the urine and intestines (48, 50, 52). Thus, although the mechanism by which dietary NT affect splanchnic blood flow is not clarified, this study confirms previous findings of higher postprandial BFV in infants fed NT-supplemented formula (27, 28).

NT are presently added to most formulas for term infants. Studies in human infants and in animals suggest that dietary NT enhance development of the gastrointestinal and immune systems (29–32), however, the mechanism of action remains unknown. Our data and those of Özkan *et al.* (28) suggest that orally administered NT are associated with effects on the intestinal vasculature.

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