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Nervonic acid is transferred from the maternal diet to milk and tissues of suckling rat pups

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Abstract

Three experiments were designed to investigate the metabolism of dietary nervonic acid (24:1n-9, NA) during reproduction in the rat. The first experiment determined the effect of early development on the sphingomyelin (SM) composition of rat heart and liver tissues. Rats were fed a standard chow diet and the SM fatty acid composition of the hearts and livers were analyzed of 18-20 day old fetuses, 14 day old sucklings and adult rats. The 18:0 content of SM decreases with age, while 23:0 and iso 24:0 increase with age. In the second experiment pregnant rats were fed diets supplemented with either canola, corn or peanut oil to determine the effect of diets high in 24:1n-9 and 24:0 on liver and heart SM at birth and after 14 days of suckling. Pups from the dams fed the corn oil diet had elevated 24:2n-6 in SM from heart and liver at birth, but the content of NA was not altered by dietary fat type. In the third experiment oil mixtures were designed to provide elevated levels of 22:1 and 24:1 (canola-N25), 22:0 and 24:0 (peanut-flax) or $<0.01\%$ of these fatty acids (olive-flax) and were supplemented to the diets of lactating rats. Canola-N25 oil supplemented to lactating rats resulted in increased 24:1n-9 and 24:1/24:0 with decreased 22:0 and 24:0 in milk SM relative to the other groups. The SM composition of livers of the suckling rats showed significant changes reflecting the changes in milk SM composition after 6 days of milk consumption. These experiments suggest that dietary NA and is not readily transferred across the placental barrier but does readily cross the mammary epithelium and is incorporated into milk SM. In addition, NA in milk appears to cross the intestinal epithelium where it is incorporated into the SM of heart and liver of suckling rats.

Keywords: Sphingomyelin; Nervonic acid; Milk; Pregnant; Rat; Diet

1. Introduction

Nervonic acid (24:1n-9, NA), like docosahexaenoic acid (22:6n-3, DHA), has been proposed to be an essential nutrient for neonatal development in humans [1–4]. Both NA and DHA are incorporated in large amounts in structural lipids in the developing central nervous system and exist in higher amounts in human milk than in bovine milk. NA supplementation has been proposed to enhance neurodevelopment in formula-fed and in premature infants [5]. Accordingly both have been proposed to be added to formulas for premature infants and term infants [1,3,4], and both are promoted as supplements during pregnancy and lactation. While substantial research has been done on DHA metabolism, the metabolism of NA during pregnancy and lactation remains obscure. Cook et al [6] have demonstrated that pregnant mice fed diets high in 22:1n-9 and 24:1n-9 had offspring that were enriched in 24:1n-9 in sphingomyelin (SM) in liver and erythrocytes. The content of the milk was very high in 22:1n-9 and 24:1n-9. Kramer et al [7,8], feeding milk replacer diets to suckling age piglets, demonstrated that milk formulas rich in 22:1n-9 would enrich cardiac and platelet SM in 24:1n-9. The experiments in the present study were designed to examine whether; maternal NA will cross the placental barrier, NA will cross the mammary epithelial barrier with incorporation into milk and milk NA can cross the intestinal barrier with enrichment of NA in tissues.

2. Materials and methods

Wistar rats (Charles River, Montreal, Que.) were housed under controlled conditions of temperature (22 C), humidity (50%), lighting (12 h day/night) and were permitted to consume food and distilled water *ad libitum*. The analytical

Abbreviations: SM; sphingomyelin; NA; nervonic acid

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methods for the phospholipid extraction, purification, transmethylation, and for the analysis of fatty acid methyl esters by gas-liquid chromatography were performed as previously described [9].

2.1. Experiment one

In the first experiment the rats were fed a standard rodent chow (Purina Lab Chow). One male rat was housed with two female rats for two days, and on the third day the females were transferred to individual cages. Five pregnant female rats of day 18-20 gestation were anesthetized with diethyl ether, decapitated and the fetuses removed, anesthetized and decapitated. From each of four litters, two pups were randomly selected after exclusion of the smallest and largest, for sacrifice and tissue dissection on day fourteen of lactation (day 14 post-partum). The remaining rats were weaned after 24 days of lactation and allowed to grow to adulthood. The male rats were sacrificed at 3 months post-weaning.

2.2. Experiment two

All rats were fed a semi-purified diet consisting of casein (20%), DL-methionine (0.3%), glucose hydrate (60%), fat (10%), cellulose (5%), choline bitartrate (0.25%) and vitamins and minerals as previously described [9]. The rats were allocated into one of three dietary groups based on the fat type: canola, corn, or peanut oil. The rats (1 male and 2 female) were placed in breeding cages, as described in experiment 1. The rats were provided the assigned diets ad-libitum throughout breeding, gestation and lactation. On the morning of the day of birth, two rats were selected as described in experiment 1 from each litter for sacrifice, tissue dissection and analysis. This also occurred on day fourteen after birth. The fatty acid composition of canola corn and peanut oils is shown in Table 1.

2.3. Experiment three

Pregnant rats (14-15 days gestation) were housed individually and fed rodent chow (Purina Lab Chow) for the remainder of gestation and for the first two days of lactation. On the third day of lactation the dams were switched to a semi-purified diet. The basal semi-purified diet was the same as in experiment two except for the fatty acid composition of the dietary fats.

The fatty acid composition of the dietary fats used in experiment 3 is shown in Table 1. The fatty acid composition of the dietary fats were designed to have similar levels of 18:1, 18:2n-6 and 18:3n-3 with either 3% of 22:0 plus 24:0 or 3% of 22:1 plus 24:1. The olive-flax mixture was designed to be a control, because it does not have detectable levels of these fatty acids. It consisted of 96.6% olive plus 3.4% flax. The Canola-N25 diet consisted of 96.6%canola plus 3.4% N-25 oil. (highly purified *lunaria biennis* oil, Croda Universal). Peanut-flax consisted of 96% peanut plus 3.4% flax.

Table 1
Fatty acid composition of dietary oils

	Experiment 2			Experiment 3		
Fatty Acid	Canola	Corn	Peanut	Canola-N25	Olive-Flax	Peanut-Flax
14:0	0.1	tr.	tr.	0.1	N.D.	tr.
16:0	6.4	12.5	13.0	6.4	18.3	13.3
18:0	1.9	1.4	2.7	1.9	2.0	2.8
18:1	66.0	31.0	51.6	66.5	60.3	51.9
18:2	20.7	54.4	27.0	20.9	19.2	27.5
18:3n-3	1.8	0.1	0.1	1.8	1.7	1.8
20:0	0.7	0.4	1.3	0.7	0.3	1.3
20:1n-9	1.5	0.2	1.2	1.6	0.2	1.1
22:0	0.3	tr.	2.3	0.3	N.D.	2.2
22:1n-9	0.6	N.D.	0.1	2.1	N.D.	0.1
24:0	0.1	N.D.	0.8	0.1	N.D.	0.8
24:1n-9	0.1	N.D.	N.D.	0.7	N.D.	N.D.
22+24C	1.1	tr.	3.2	3.2	N.D.	3.1

Values are means of n = 3 expressed as mol%. Tr. < 0.05 mol%. N.D. < 0.01mol%. Canola-N25 consisted of 96.6% canola plus 3.4% N-25, Olive-flax consisted of 96.6% olive plus 3.4% flax, peanut-flax consisted of 96% peanut plus 3.4% flax.

Pups were selected as described in experiment 1 and sacrificed after 0, 2, 6, 10, and 14 days of nursing from dams fed the different diets. Gastric milk was harvested from all pups and livers were harvested from pups sacrificed on days 0, 6 and 14.

3. Results

Table 2 shows that numerous changes occurred in the fatty acid composition of SM of heart and liver during development. The content of 16:0 increased at suckling in the liver and heart relative to both the fetal and adult stage; 18:0 decreased at suckling and further decreased in adults in both the heart and liver. The content of 20:0 decreased at the suckling stage in the liver and heart, while 22:0 decreased at suckling and then increased in adults in both heart and liver. Both 23:0 and iso 24:0 increased at suckling and again in the adults. The content of 24:0 increased at suckling and again in adults in liver, it increased in adults in the heart. In adult liver, 24:1n-9 decreased while 24:2n-6 increased. Both 24:1n-9 and 24:2n-6 showed decreases in the suckling stage and increases in the adult stage.

Table 3 shows that newborn rats whose mothers were supplemented with the corn oil diets had dramatic decreases in liver 16:0. Newborn rats of corn oil supplemented dams also had higher levels of 24:1n-9 than the pups born to peanut oil supplemented dams. Dietary fat type did not affect the ratio of 24:1/24:0 in newborn rat liver. The canola oil supplemented 14 day old rats had higher 24:1n-9 than the peanut oil supplemented newborns and a higher ratio of 24:1/24:0 than the corn or peanut supplemented groups.

Table 2
Sphingomyelin fatty acid composition of rat livers and hearts of fetal, suckling and adult rats fed chow diets (experiment 1)

	Liver			Heart		
Fatty Acid	18-20 day fetus	14 days old	4 months old	18-20 day fetus	14 days old	4 months old
16:0	18.0[a]	28.1[b]	18.6[a]	22.2[a]	42.4[b]	14.4[c]
18:0	25.0[a]	14.7[b]	4.7[c]	20.5[a]	17.4[b]	15.1[c]
18:1	1.8[b]	3.8[a]	0.7[b]	2.0	6.9	2.5
18:2	0.3	1.0	0.7	0.4[a]	1.5[b]	1.0[a,b]
20:0	6.8[a]	1.9[b]	1.6[b]	17.4[a]	8.5[b]	11.7[b]
22:0	17.5[a]	5.8[b]	9.3[c]	11.2[a]	6.3[b]	14.9[c]
23:0	0.9[a]	5.1[b]	10.5[c]	0.5[a]	2.1[b]	8.7[c]
Iso 24:0	0.3[a]	1.1[a]	4.1[b]	N.D.[a]	0.6[b]	1.6[c]
24:0	11.9[a]	22.6[b]	30.3[c]	9.5[a]	7.3[a]	17.1[b]
24:1n-9	16.1[a]	14.0[a,b]	14.0[b]	13.8[a]	6.2[b]	10.5[c]
24:2n-6	1.4[a]	2.0[a]	4.4[b]	2.6[a]	0.6[b]	2.5[a]
24:1/24:0	1.36[a]	0.62[b]	0.51[c]	1.59[a]	0.86[a,b]	0.62[b]

Values are means expressed as mol%. N.D. $<$ 0.01mol%. Comparisons were done between different stages of development within liver or heart using Tukey's test (18-20 day fetus n = 5, 14 days old n = 4, 4 months old n = 3). Significant differences are indicated by different letters ($P < 0.05$).

Table 4 shows that the hearts of newborn rats whose mothers were supplemented with corn oil had decreased in 16:0 compared to the other diets. 18:0, 20:0 and 24:2-n6 were increased in the newborns of the corn oil supplemented diets compared to both the newborns of both the canola and peanut oil supplemented dams. The 24:1/24:0 ratio was increased in the newborns of the canola oil supplemented dams.

Table 4 also shows that the pups suckling from the peanut oil supplemented dams had lower 20:0 and higher 22:0 and 24:0 than either of the other two groups of pups. Sucklings of the canola oil supplemented dams had higher levels of 24:1n-9 than either of the other two groups. Dietary fat type significantly affected the 24:1/24:0 ratio, with canola higher than corn and corn higher than peanut. 24:2n-6 was higher in the sucklings of the corn oil supplemented dams than either of the other two groups.

The peanut-flax oil supplementation resulted in increased 24:0 SM in the milk with decreased 24:1n-9 and 24:1/24:0 relative to the other two groups at day 2 (Table 5). Milk from the canola-N25 supplemented group had increased 24:1n-9. Again dietary fat type significantly affected the 24:1/24:0 ratio, at three levels of significance (canola-N25 $<$ olive-flax $<$ peanut-flax). These effects continued after 14 days of supplementation.

Peanut-flax oil supplementation resulted in increased 24:0 SM in the livers of sucklings compared to the other two groups after 6 days of supplementation (Table 6). The canola-N25 supplemented group resulted in an increase in 24:1n-9 relative to the other two groups. These effects

Table 3
Sphingomyelin fatty acid composition of rat livers at birth and after 14 days of suckling. Dams were supplemented with either canola, corn or peanut oil throughout gestation and lactation (experiment 2)

	Newborn			14 days old		
Fatty Acid	Canola	Corn	Peanut	Canola	Corn	Peanut
16:0	19.7[a]	4.2[b]	20.5[a]	27.9	17.0	27.9
18:0	17.8	11.6	18.2	7.5	10.3	5.2
18:1	7.5	7.4	6.9	0.9	2.3	2.3
18:2	1.2	1.3	1.7	0.9	0.9	1.4
20:0	5.4	6.3	4.7	2.0	2.6	3.5
22:0	14.8	18.0	15.1	7.5	8.5	8.5
23:0	1.4	1.5	1.2	3.4	4.8	3.1
Iso 24:0	0.6	0.2	0.4	1.5	3.5	1.9
24:0	12.8	18.0	14.9	27.5	32.7	35.1
24:1n-9	16.8[a,b]	26.3[a]	14.8[b]	20.1[a]	14.8[a,b]	10.7[b]
24:2n-6	1.5[a]	5.2[b]	1.5[a]	0.7[a]	2.7[b]	0.5[a]
24:1/24:0	1.32	1.45	1.06	0.73[a]	0.47[b]	0.32[b]

Values are means of n=3, expressed as mol%. N.D.$<$0.01mol%. Comparisons were done between different diets at birth and after 14 days of suckling, using Tukey's test. Significant differences are indicated by different letters ($P < 0.05$). Values of 24:2n-6 for newborn rats were significantly different by Duncan's Multiple range test ($P < 0.05$).

Table 4
Sphingomyelin fatty acid composition of rat hearts at birth and after fourteen days of suckling. Dams were supplemented with either canola, corn or peanut oil throughout gestation and lactation (experiment 2)

	Newborn			14 days old		
Fatty Acid	Canola	Corn	Peanut	Canola	Corn	Peanut
16:0	40.5[a]	15.4[b]	36.7[a]	25.7[a]	24.4[a,b]	20.7[b]
18:0	16.2[a]	24.1[b]	16.4[a]	13.9[a,b]	17.4[a]	13.3[b]
18:1	3.4	0.4	0.3	0.3	0.5	0.6
18:2	1.8	N.D.	0.7	0.6	0.8	0.6
20:0	12.2[a]	20.8[b]	13.8[a]	17.4[a]	17.0[a]	12.6[b]
22:0	7.7[a]	11.2[b]	10.1[a,b]	13.5[a]	13.0[a]	21.3[b]
23:0	0.3	0.7	0.3	2.1[a,b]	2.5[a]	1.7[b]
Iso 24:0	N.D.	N.D.	N.D.	0.5	0.6	0.3
24:0	6.5[a]	10.8[b]	8.9[a,b]	9.8[a]	11.8[b]	18.9[c]
24:1n-9	10.4	13.2	11.3	15.3[a]	9.3[b]	8.9[b]
24:2n-6	1.0[a]	3.4[b]	1.4[a]	0.9[a]	2.6[b]	1.1[a]
24:1/24:0	1.60[a]	1.22[b]	1.26[b]	1.57[a]	0.80[b]	0.48[c]

Values are means of n=3, expressed as mol%. Comparisons were done between different diets at birth and after 14 days of suckling, using Tukey's test. Significant differences are indicated by different letters ($P<0.05$).

continued after 14 days of supplementation. The ratio of 24:1/24:0 increased in the canola-N25 supplemented group after 6 days of supplementation which continued after 14 days of supplementation. The peanut-flax supplemented group showed a decreased ratio of 24:1/24:0 only after 14 days of supplementation. The effects were similar on days 6 and 14 of lactation, however the olive-flax group had significantly more 16:0 SM than the peanut-flax group on day 14.

4. Discussion

The metabolism of NA has been reported to be altered in a number of conditions, including cystic fibrosis [10], multiple sclerosis [11], schizophrenia [12], peroxisomal disorders [13–15], and other conditions [16–20]. However it is not clear how NA is metabolized during normal development.

Experiment 1, which determined the effect of early development on the SM composition of rat heart and liver tissues, demonstrates that there are substantial developmental effects on the fatty acid composition of SM in the rat. The rats were fed a common laboratory chow, a practical diet adequate for growth and reproduction in rats. This diet is commonly used to feed rats in commercial breeding, research laboratory and residential facilities. The largest and most consistent effects in heart and liver are the decrease in 18:0 and the increase in 23:0, iso 24:0 and 24:0 from birth

Table 5
Sphingomyelin fatty acid composition of gastric milk of sucklings, nursing from dams fed diets supplemented with canola-N25, olive-flax or peanut-flax oils throughout lactation (experiment 3)

	Time 0 (2 days old)	2 Days of Supplementation (4 days old)			6 Days of Supplementation (8 days old)		
Fatty Acid	Chow	Canola-N25	Olive-Flax	Peanut-Flax	Canola-N25	Olive-Flax	Peanut-Flax
16:0	23.1	16.2	22.9	17.9	16.3	18.8	19.0
18:0	6.0	4.0	3.5	2.8	2.4	2.9	3.3
18:1	1.0	1.9	2.2	1.1	1.7	5.6	1.7
18:2	0.4	0.5	0.8	0.8	1.2	2.2	1.1
20:0	1.7	1.1[a,b]	1.4[a]	0.8[b]	1.1	1.6	0.8
22:0	10.1	8.5[a]	11.1[a,b]	14.3[b]	6.6[a]	10.4[b]	14.9[c]
23:0	7.2	4.3[a]	8.3[b]	4.6[a]	2.2[a]	4.6[b]	2.0[a]
Iso 24:0	0.6	0.6	0.6	0.4	0.7	1.5	0.2
24:0	20.6	18.4[a]	20.8[a]	41.1[b]	16.2[a]	21.9[a]	42.5[b]
24:1n-9	28.2	43.9[a]	26.8[b]	15.6[c]	50.6[a]	29.3[b]	13.8[c]
24:2n-6	1.2	0.7	1.4	0.6	1.1	1.2	0.6
24:1/24:0	1.36	2.39[a]	1.36[b]	0.38[c]	3.16[a]	1.39[b]	0.33[c]

Values are means of $n = 4$, except for day 0 which has $n = 15$. Values are expressed as mol%. Comparisons were done between different diets after two and six days of supplementation using Tukey's test. Significant differences are indicated by different letters ($P < 0.05$). Time 0 of the experiment = day 2 postpartum.

Table 6
Sphingomyelin fatty acid composition of livers of suckling rats nursing from dames supplemented with canola-N25 oil, olive-flax or peanut-flax throughout lactation (experiment 3)

Fatty Acid	Time 0 (2 days old)	6 Days of Supplementation (8 days old)			14 Days of Supplementation (16 days old)		
	Chow	Canola-N25	Olive-Flax	Peanut-Flax	Canola-N25	Olive-Flax	Peanut-Flax
16:0	31.2	22.9	32.1	26.4	27.4[a,b]	35.5[a]	20.7[b]
18:0	21.2	11.6[a]	22.3[b]	12.6[a]	13.7[a]	22.4[b]	11.5[a]
18:1	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
18:2	0.3	2.5	0.2	0.3	0.2	0.2	0.2
20:0	2.6	3.7	2.7	2.2	2.5	3.4	2.4
22:0	8.8	6.5[a]	8.4[a,b]	10.2[b]	4.9[a]	9.8[b]	11.8[b]
23:0	3.4	1.6	3.4	2.0	1.4[a]	3.6[b]	2.2[b]
Iso 24:0	0.1	0.4[a,b]	1.1[a]	0.2[b]	0.8	0.8	0.8
24:0	12.6	12.7[a]	15.1[a]	32.1[b]	13.9[a]	13.8[a]	35.6[b]
24:1n-9	19.3	37.4[a]	13.7[b]	13.4[b]	34.7[a]	9.9[b]	13.7[b]
24:2n-6	0.5	0.6	1.1	0.8	0.6	0.7	1.2
24:1/24:0	1.55	2.92[a]	0.93[b]	0.42[b]	2.49[a]	0.74[b]	0.39[c]

Values are means of n = 3, expressed as mol%. N.D. < 0.01mol%. Comparisons were done between different diets after six and fourteen days supplementation using Tukey's test. Significant differences are indicated by different letters ($P < 0.05$).

to early adulthood. The concentration of NA in SM of heart and liver does not change consistently with age, however, there is a significant drop in the NA content of heart during the suckling period. Overall, there is a steady drop in the 24:1/24:0 ratio with age in both tissues. This ratio has been previously demonstrated to be highly sensitive to dietary intake of 22:1, 24:1 and 24:0 in weanling [21] and adult [22] rats.

Experiment 2, where different oil mixtures were supplemented to the diets of lactating rats to determine the effect diets high in 24:1n-9 and 24:0 on liver and heart SM at birth and after 14 days of suckling, suggests that neither 24:0 or 24:1 readily cross the placental barrier and appear in pup tissues at birth. The rats sacrificed on day 0 were full term pups (estimated 4-8 hr old) that may have consumed some colostrum before sacrifice. Even so, both the peanut oil-fed rats (a source of in 22:0 and 24:0) and the canola-oil fed rats (a source of 22:1 and 24:1) have similar 24:1 to 24:0 ratios in heart and liver when compared to pups from corn oil fed dams (very low in these fatty acids) and when compared to late fetal rat pups from dams fed laboratory chow (compare results in Tables 2 and 3). The small but significant differences in the 24:1/24:0 ratios between canola fed rats and those from the corn oil and peanut oil treatments may be due to the higher intake of 18:1n-9 in the canola oil group. Oleic acid (18:1n-9) is known to cross the placental barrier [23] and has been shown in adult rats to contribute to the 24:1/24:0 ratio in tissues [21].

The second experiment also suggests that 24:1n-9 and 24:0 appear in milk in a form which is bioavailable to the offspring. Maternal intake of 22:1 and 24:1n-9 or (22:0 and 24:0) leads to major shifts in the ratio of 24:1/24:0 in tissues of 14 day old rats, as it does in weanling rats consuming semi-purified diets. The effect of dietary corn oil on the 24:2n-6 content of SM in the tissues of 14 day old rats continues the trend seen at birth. It is not known if the effect is mediated via 18:2n-6 or 24:2n-6 in the milk.

In experiment 3, different oil mixtures were supplemented to the diets of lactating rats to clarify the effects of 22:0, 22:1n-9, 24:0 and 24:1n-9 in the maternal diet on the accumulation of these fatty acids in the suckling rat. Dietary 24:1n-9 and 24:0 are enriched in rat milk SM within two days of ingestion of the appropriate diets. The effect is maximal within six days of commencing the diet; similar levels were attained at day 10 and 14 of lactation (data not shown). The 24:1n-9 to 24:0 ratio of SM in heart and liver of lactating pups depends on milk fatty acid composition; milk 22:0, 24:0 and 24:1n-9 fatty acids are highly bioavailable to suckling rat pups. NA in milk appears mainly as sphingomyelin, suggesting that nervonyl-SM is a source of bioavailable NA under these physiological conditions.

In conclusion, NA does not appear to readily cross the placental barrier in the rat. However, it crosses the mammary epithelial barrier, where it appears as nervonyl-SM of the milk fat globule membrane. Similarly, milk NA crosses the epithelial barrier of the intestine of rat pups and accumulates in the heart and liver as nervonyl-SM. The lack of permeability of NA to the placental barrier, while retaining the ability to cross mammary epithelium and intestinal epithelium differs from the metabolism of DHA. DHA crosses the placental barrier in the third trimester of pregnancy [23,24]. Additional research on the post-prandial metabolism of NA from milk is warranted, along with possible interactions between DHA and NA metabolism.

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