Original Article

Metabolic fate of intravenously administered *N*-acetylneuraminic acid-6-^{14}C in newborn piglets

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Background: Sialic acid (*N*-acetylneuraminic acid), a component of gangliosides and sialylglycoproteins, may be a conditional nutrient in early life because endogenous synthesis is limited. The aim of this study was to investigate the metabolic fate of intravenously administrated *N*-acetylneuraminic acid 6^{14}C (sialic acid) in piglets. Method: Three-day-old male domestic piglets (*Sus scrofa*) were injected via the jugular vein with 5 μCi (11-12x10^6 cpm) of *N*-acetylneuraminic acid-6^{14}C (specific activity of 55 mCi/mmol). Blood samples were collected at regular intervals over the next 120 min. The organs were then removed and the urine collected for determination of residual radioactivity. Results: Within 2 min of injection, 80% of the activity was removed from the blood and by 120 min the remaining activity approached 8%. At 120 min, the brain contained significantly more radioactivity (cpm/g tissue) than the liver, pancreas, heart and spleen, but less than the kidneys. Within the brain, the percentage of total injected activity was highest in the cerebrum (0.175 ± 0.008) followed by the cerebellum (0.0295 ± 0.006, p = 0.00006) and the thalamus (0.029 ± 0.006, p = 0.00003). Conclusions: An exogenous source of sialic acid is capable of crossing the blood-brain barrier and being taken up into various tissues. The findings suggest that dietary sources of sialic acid may contribute to early brain development in newborn mammals.

Key Words: ***N*-acetylneuraminic acid 6 ^{14}C, intravenous administration, brain, metabolic fate, newborn piglets**

Introduction

Sialic acids are negatively charged monosaccharides attached to the end of sugar chains, giving rise to a wide variety of glycoproteins and glycolipids in biological fluids and cell membranes. As cell-surface glycoconjugates, they are directly involved as receptors in cell-to-cell, cell-to-microorganism, cell-to-toxin and cell-to-antibody binding.[1] In human milk, sialylated oligosaccharides act as highly specific receptors for a variety of viruses, bacteria and parasites.[2] Sialic acids are also a structural component of brain gangliosides and sialoglycoproteins, playing a key role in the functional establishment of synaptic pathways.[3-5] The acidic nature of sialic acids creates a negative charge on the cell membrane, facilitating the binding of positively charged neurotransmitters.[6]

Sialylated proteins such as neuron cell adhesion molecule (NCAM) are involved in a wide range of morphogenic events, including cell migration, neurite outgrowth, sprouting, regeneration and synaptic plasticity.[7-9] Higher learning and memory in rodents is associated with an increase in NCAM sialylation state in the brain[10] and NCAM polysialylation regulates neural plasticity during growth and aging.[11]

These findings give rise to the hypothesis that supplementary sialic acid may enhance memory and learning. In rodents, exogenous sources of sialic acid have been shown to influence brain growth and learning ability.[12,13] While all mammals have the capacity to synthesise sialic acid from simple sugar precursors, the liver of the human infant is relatively immature and may not be capable of synthesising the full requirements for rapid growth and development.[14,15] It may not be coincidental that human milk is a particularly rich source of sialic acid, capable of supplementing limited endogenous synthesis.[15] At the present time, however, the precise details of the absorption and metabolism of human milk oligosaccharides are unknown.

To date, most researchers have employed rats and mice to explore the absorption, transport, site and function of sialic acid.[16-18] For nutrition studies, however, piglets are a better animal model. Due to physiological and anatomical similarity of the human and pig digestive tract, piglets resemble the human neonate in more ways than other non-primate mammalian species.[19] Most importantly, they

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have similar nutrient requirements and in both species (unlike rodents), birth occurs in the midst of the developmental spurt of brain-mass accretion.[20]

The aim of this study was to investigate the metabolic fate of intravenously administrated *N*-acetylneuraminic acid 6^{14}C (free form sialic acid) in newborn piglets. We were particularly interested to determine whether sialic acid could cross the blood-brain barrier and whether it was taken up more readily in regions of the brain devoted to cognition. The study formed part of our effort to evaluate the neonatal pig as a model for investigation of the role of supplementary sialic acid in enhancing learning and memory.

Method

Subjects and jugular vein catheterisation

Four 3-day-old male domestic piglets (*Sus scrofa*) were obtained from 2 litters at a commercial pig farm (Menangle NSW) and kept at 30°C. The piglets were fasted for 3 hours and then anaesthetized by 4% isoflurane (Abbott Australia, Kurnell NSW) in oxygen. A Flurotec-3 vaporiser (Cyprane, England) with a flow rate of 1.0 L/min was used to deliver the gases. The isoflurane concentration was regulated throughout the procedure according to the reflex responses of the individual piglets. An incision was made in the neck from the scapulohumeral joint to a point slightly above the angle of the jaw on the vertical ramus of the mandible. After exploration and isolation of the jugular vein, 2 ligatures were placed at the extremities of the cleared vein to halt blood flow prior to cutting the vein. A catheter, filled with heparinized saline (Baxter Healthcare, Toongabbie NSW), was inserted through the incision into the vein for 5-8 cm. The ligature closest to the heart was tied around the catheter and the vein was excluded at the cranial end with the remaining ligature. The incision was closed and the catheter was secured in position by a protective bandage. Post surgery, the piglets were placed in single pens and allowed to recover in a room maintained at 30°C. Water and feed were withheld. The study was approved by the University of Sydney animal ethics committee.

Intravenous administration of N-acetylneuraminic acid 6 ^{14}C

Two hours post surgery recovery, each piglet was given a bolus infusion of 5 µCi (11-12x10^6 counts per min (cpm) of *N*-acetylneuraminic acid-6^{14}C (Sigma Aldrich, Castle Hill, NSW) with a specific activity of 55 mCi/mmol. This was immediately followed by 5 ml saline to clear any radioactivity remaining in the infusion line. The mean quantity of labelled sialic acid received by the piglets was 2.78 µCi/kg.

Blood sample and organ collection

Blood samples (1 mL) were taken from each piglet at 0, 2, 5, 10, 20, 30, 45, 60, 75, 90, 105 and 120 minutes post-infusion. Following each sampling, the catheter was flushed with heparinized saline (approximately 5ml). The samples were centrifuged at 2300 rpm for 15 min at 4°C. The plasma was removed and stored at –20°C until analysis. After the final blood sampling, the piglets were euthanased using an overdose of pentobarbitone solution (Valabarb; Jurox, Silverwater, Australia). Brain, liver, lungs, kidneys, heart, pancreas and spleen were removed and weighed. The bladder was removed, the urine was collected and weight determined. The brain tissues were dissected into frontal lobe, right and left cerebrum, cerebellum, thalamus and weighed separately. All organs were placed in airtight containers and stored at -20°C until analysis.

Radioactivity measurement

Duplicate tissue samples were weighed and digested in Soluene 350 (Packard, PerkinElmer, Rowville Victoria, Australia) by incubating at 35°C overnight. Upon complete digestion of the tissue, 3 mL of scintillation cocktail (Hionic-Fluor: Packard, PerkinElmer, Rowville Victoria, Australia) was added and the radioactivity determined as counts per minute (cpm) using a beta scintillation counter (LKB Wallac, Turku, Finland). The radioactivity in duplicate 100 µL plasma samples was also determined after automatic correction to 100% efficiency in the ^{14}C-radioactivitites. Nohle (1984) demonstrated that the radioactivity measured in the various tissues was actually intact ^{14}C-labeled *N*-acetylneuraminic acid using thin-layer chromatograph.

Statistical analysis

Differences in the radioactivity accumulated in various organs and tissues were determined using ANOVA with site and individual pig as factors, and with Bonferroni adjustment for multiple comparisons. A logarithmic scale was used to ensure that the assumptions of homoscedasticity were satisfied, although the summary statistics are reported on the ordinary scale. Urine was not included in these models as a "site" since all urine values were several orders of magnitude higher than any other values. To investigate the time effect on level of radioactivity of sialic acid in plasma after intravenous administration, data from all four pigs was used to estimate a profile for the decline in radioactivity over time. Differences at individual timepoints were investigated using post hoc ANOVA tests with Bonferroni adjustment for multiple comparisons. All analysis was completed using SPSS for Windows 11.0 (SPSS Chicago). The significance level was set at $p < 0.05$.

Results

Body weight and organ weight

Mean body and organ weights are shown in Table 1. The liver was the heaviest organ collected (4.1% of total body weight), followed by the lungs and brain (3.4% and 1.7% respectively).

Plasma radioactivity

Overall, about 80% of the administered activity was removed from the circulation 2 min post- injection. Plasma levels fell rapidly in the first 5 min and then remained relatively constant in all piglets. All 4 piglets displayed the same temporal pattern of excretion ($p = 0.0001$, Fig 1), with no significant differences between the individual piglets at any time point ($p > 0.05$). At 120 min, the remaining *N*- acetylneuraminic acid 6^{14}C represented about 8% of the administered dose.

Table 1. The mean body weigh and organ weight

	n	Mean weight (g)	SD
Body weight	4	1840	290
Brain	4	31.6	2.46
Liver	4	74.7	18.73
Pancreas	4	2.4	0.45
Spleen	4	3.6	0.42
Right Kidney	4	7.8	0.74
Left Kidney	4	7.9	0.57
Lung	4	61.8	25.32
Heart	4	12.7	2.41

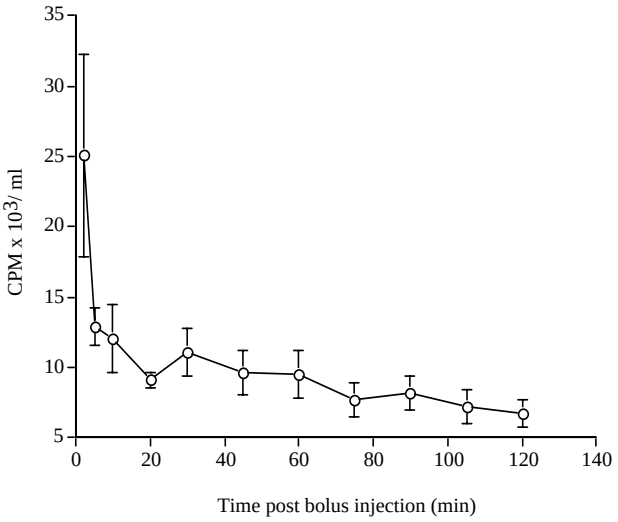

Figure 1. Time trend (mean ± SE) of radioactivity in plasma 2 h after intravenous injection of *N*-acetylneuraminic acid-6^{14}C to the newborn piglets (n=4 at all timepoints). There were highly significant changes with time (p<0.0001).

Brain radioactivity

Uptake of labelled sialic acid into the different segments of the brain is shown in Table 2. Total activity (cpm) was highest in the cerebrum (20145 ± 2425) followed by the cerebellum (3412 ± 697) and the thalamus (3315 ± 613), the differences being highly significant (p = 0.000). Even the individual parts of cerebrum, such as the left cerebrum, right cerebrum and frontal lobe were also higher than the total radioactivity in the cerebellum and thalamus. Taken together approximately 0.23% of the total dose of labelled sialic acid was incorporated into the brain within 120 min of administration.

Other organs

The mean level of radioactivity detected in other organs is shown in Table 3. Compared with the brain, the radioactivity (cpm per gram tissue) was significantly lower in the liver (p= 0.0001), pancreas (p= 0.002), spleen (p= 0.00002) and heart (p= 0.001). There was no difference between the brain and lungs (p= 0.3). The kidneys however, contained more than twice the activity of the brain (p= 0.001). Overall about 5% of the injected activity of ^{14}C-sialic acid remained in the organs 120 min after administration, most of it in the lungs and liver. The collected urine contained 45% of the injected activity.

Discussion

The present study describes the fate of intravenously administrated sialic acid in piglets. Our findings indicate that free sialic acid is taken up into the organs and crosses the blood-brain barrier, implying that an exogenous source of sialic acid may be important to brain growth. The majority of the label was incorporated into the cerebrum rather than cerebellum and thalamus, suggesting that cerebral neurons may use exogenous sources of sialic acid to build sialylated glycolipids (gangliosides) and glycoproteins (NCAM).

Table 2. The mean uptake (mean ± SEM) of labelled sialic acid into the brain segments of 3 day-old piglets

Brain segment	n	Activity (cpm/g)	Total activity (cpm)	Percentage of injected activity
Frontal lobe	4	920 ± 226	5274 ± 1109	0.05 ± 0.01
Left cerebrum	4	804 ± 106	7650 ± 781	0.07 ± 0.01
Right cerebrum	4	814 ± 107	7222 ± 688	0.06 ± 0.01
Total cerebrum	4	2537 ± 421*	20145± 2425*	0.18 ± 0.02*
Cerebellum	4	996 ± 236	3412 ± 697	0.03 ± 0.01
Thalamus	4	945 ± 204	3315 ± 613	0.03 ± 0.01

Data in the same column with asterisk are statistically different between others (p< 0.05).

Table 3. The mean uptake (mean ± SEM) of labelled sialic acid into the major organs of 3 day-old piglets

Tissue	n	Activity (cpm/g)	Total activity (cpm x 10^3)	Percentage of injected activity
Brain (whole)	4	4478 ± 856[a]	26.87 ± 3.72[a]	0.23 ± 0.03 [a]
Lungs	4	3246 ± 458[ab]	183.86 ± 22.00[b]	1.59 ± 0.18 [b]
Liver	4	2260± 369[b]	163.72 ± 20.49[b]	1.42 ± 0.19 [b]
Heart	4	2411 ± 371[b]	29.43 ± 2.24[a]	0.25 ± 0.02 [a]
Spleen	4	2124 ± 433[b]	7.27 ± 1.12[d]	0.06 ± 0.01 [d]
Pancreas	4	2594 ± 529[b]	5.92 ± 0.61[d]	0.05 ± 0.01 [d]
Left kidney	4	13092 ± 2862[c]	103 ± 23[c,b]	0.89 ± 0.21 [c,b]
Right kidney	4	11570 ± 1585[c]	91.16± 15.73[c]	0.79 ± 0.14[c]

Data in the same column with different letters are statistically different ($p< 0.05$)

In piglets, the pattern of sialic acid excretion differed from that seen in other animal models. Levels in plasma fell dramatically within the first 20 mins of administration, with only 8% remaining after 2 h. This rate of excretion was slower than that of adult rats which excreted more than 99% within the same timeframe.[17] However, 3 day-old rat pups given an oral dose of *N*-acetyl ^{14}C neuraminic acid, excreted only 70% within 6 h.[16] In the bound form of ^{14}C-sialyllactose, maximum radioactivity in the plasma was attained after 3 h.[16] These findings suggest that the metabolism of sialic acid may depend not only on the species and age but also on the method of administration and the form in which the sialic acid is presented, ie whether free or bound. We deliberately chose the intravenous route and free form, so that the sialic acid could be directly transported to the organs and tissues and not affected by digestion or absorption. Moreover, we studied very young animals because brain growth is most rapid at that stage and uptake more likely.

Our most important finding is that the radioactivity of sialic acid per gram of tissue was significantly higher in the brain than any other organ, except for the kidneys ($p< 0.05$). This infers that free sialic acid can pass through the blood-brain barrier and be incorporated into brain tissue. As we administrated a very large bolus dose intravenously, excess sialic acid is likely to be transported directly to the kidneys in efforts to re-establish homeostasis. Thus the higher activity per gram tissue in the kidneys is not unexpected. Other than the kidneys, the rank order of uptake was brain (4478 cpm/g) followed by the lungs (3246 cpm/g), pancreas (2594 cpm/g), heart (2411 cpm/g), liver (2260 cpm/g) and spleen (2124 cpm/g). The difference between the organs in uptake and incorporation of *N*-acetylneuraminic acid 6^{14}C was highly significant ($p<$ 0.05 - 0.001), suggesting that the central nervous system might 'require' significantly more sialic acid per gram of tissue than other organs. In the adult human, the concentration of sialic acid in grey matter is approximately 15 times higher than in larger visceral organs such as the lungs, liver and spleen, and 500 times greater than the intestinal mucosa.[21]

Although a high level of labelled sialic acid was recovered in the piglet brain, distribution was not uniform (Table 2). About 60% was incorporated into the cerebrum and less than 15% into the cerebellum and thalamus. The different areas of brain have different neurological functions. The part responsible for high level cognitive ability is the cerebral cortex. It is possible that this area takes up more sialic acid in order to biosynthesise greater quantities of gangliosides and sialylglycoproteins. In the cerebral cortex of animals, there is a clear evolutionary trend in rank order of ganglioside concentration (rat, mouse, rabbit, sheep, cow and chimpanzee), with the highest level in the human brain.[22]

Rodent models are often use as the first choice for metabolic studies because they are easy to handle and inexpensive to maintain. However, in some experiments the age of the animal was relatively high (30 days) and possibly unsuitable from the viewpoint of brain growth. In adult rats, intravenous injection of doubly labelled *N*-acetylneuraminic acid 2^{14}C, 9^{3}H[17] resulted in less than 0.05% of the labelled dose of ^{14}C and 0.16% of ^{3}H in the brain after 2 h. By contrast, in rat pups, 1% (ie 20 times more) of the labelled sialic acid was recovered in the brain after 2 h and 0.5% after 6 h.[17] The level of incorporation into the brain of newborn piglets is therefore higher than the 30-day-old rats (0.23% vs 0.05%) but lower than that of 3 day-old rats (0.23% vs 1%). The latter difference might be explained by the two modes of administration (intravenous vs oral). It is possible that oral dosing is associated with slower absorption and therefore less rapid removal from the bloodstream than occurs with bolus intravenous administration.

Uptake and incorporation of *N*-acetylneuraminic acid 6^{14}C among the remaining organs is also of interest. The percentage of total activity in the liver was higher in the

piglet than the adult rat (eg 1.42% vs less than 0.5%).[17] Since both studies used the same route of administration, isotope and dose, the different ages may indicate differences in sialic acid 'requirement'. The rapid clearance of labelled sialic acid from the circulation, coupled with 44% of the total injected activity found in the urine, suggests that free sialic acid may be directly taken up into the organs without chemical alteration. The final level of radioactivity in the large organs of piglets was only 5% of the injected activity, but this excludes the muscle mass and bone uptake, which were not evaluated. It is possible that the lungs excrete quantities of radioactivity during respiration. For example, in mice, 15% of the ^{14}C-radioactivity is expired in the breath within 10 h of administration of labelled sialyllactose.[17]

This experiment provides objective evidence in a large animal model that an exogenous source of sialic acid can be taken up by the brain and other organs. Further studies are required to determine the contribution of dietary sources of sialic acid to the structure and function of the brain in animals capable of high level cognitive processing. Further studies are required to determine whether dietary sources of sialic acid including oligosaccharide-bound, protein-bound or lipid-bound forms can be digested absorbed and incorporated into brain gangliosides, and–glycoproteins to influence cognitive processing.

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以静脉注射放射性 6-^{14}C 标记的 N-乙酰神经氨酸在新生猪里的代谢情形

摘要：唾液酸(Sialic Acid)(*N*-acetylneuraminic acid，N-乙酰神经氨酸)是神经节苷脂(ganglioside)和唾液酸糖蛋白(sialylglycoprotein)的组成成分之一。在生命初期，因为内源合成的唾液酸有限，唾液酸可能是一种重要的条件营养素。该研究的目的是调查经静脉注射、带放射性6-^{14}C标记的N-乙酰神经氨酸(唾液酸)在新生猪里的代谢途径。方法：通过颈静脉注射5 μCi (11-12x106 cpm)的6－^{14}C-N-乙酰神经氨酸(比活度为55 mCi/mmol)到三天大的雄性新生猪（*Sus scrofa*）里。在注射后的120分钟内定时抽取血样。120分钟后取出器官并且收集尿样来测定残留的放射性。结果：在注射后两分钟内，血样中的放射性的6－^{14}C标记的N-乙酰神经氨酸减少了80%，而在120分钟后，血样中残余的放射性下降至接近8%。在注射后120分钟的时候，脑部里的放射性(cpm/g 组织)比肝脏、胰腺、心脏和脾里的放射性显著要高，但是却比肾脏里的要低。在脑部里，大脑含有注射的总放射性的百分比最高(0.175±0.0080)，随之是小脑(0.0295±0.006, p= 0.00006)和丘脑(0.029±0.006, p= 0.00003)。结论：外源性游离唾液酸可以穿过血脑屏障(blood brain barrier)并且可以进入各种组织。这些发现表明从饮食中摄取的唾液酸可能有助于新生哺乳动物的早期脑部发育。

關鍵字：N-乙醯神經氨酸 6^{14}C，静脈注射，大腦，代謝情形、新生小豬。