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THE ROLE OF ANIMAL MODELS IN UNDERSTANDING FEEDING BEHAVIOR IN INFANTS

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ABSTRACT

The common evolutionary history humans share with mammals provides us with a solid basis for understanding normal oropharyngeal anatomy and functions. Physiologically, feeding is a cycle of neurophysiologic activity, where sensory input travels to the CNS which sends motor signals out to the periphery. Research with animal models is valuable because it is possible to disrupt this cycle, and develop predictive models on the causal basis of deviation from normal. Based on work with animal models, normal mammalian infant feeding behavior consists of the tongue functioning as a pump. First, the tongue assists in acquisition of milk from the nipple into the oral cavity, and then it pumps milk from the oral cavity into the valleculae prior to the pharyngeal swallow. Starting with this basic model, feeding in infant pigs was manipulated to determine the impact of variation in sensory input on behavioral output. One set of experiments suggested that chemo- or liquid sensation, in the form of milk is necessary to elicit continuing rhythmic activity. However, the rates of rhythmic suckling are intrinsic to an animal, and variation in rate cannot be entrained. Another set showed that initiation of the swallow does not purely depend on the volume of milk delivered, but also on the sensory stimulation at the mouth. These results support the idea that feeding behavior involves complex sensory integration.

KEY WORDS: Animal models, Feeding behavior, Infant

A COMPARATIVE/ EVOLUTIONARY PERSPECTIVE FOR CLINICIANS

Humans are unique, but they share an evolutionary history with all mammals (Darwin, 1859). Insight into that history provides us with a solid basis for understanding both normal oropharyngeal anatomy as well as the myriad of functions of that anatomy. Human anatomy is not optimally designed, and history can suggest which configurations are the results of the constraint of evolutionary ancestry. Function, too, has an evolutionary history (Schwenk, 2000). Much of the physiology that is critical for normal function is also not optimally formed in humans, including those aspects of physiology that are common with other mammals. This lack of optimality is even more apparent when the physiology is disrupted in pathology.

As evidenced by the fossil record and comparative studies of living mammals, a number of correlated and interrelated traits originated with mammals. Most of these traits are related, either functionally or historically to endothermy, or "warm-bloodedness". Endothermy places a high metabolic demand on any organism (Schmidt-Nielsen, 1979). Those energy demands must be met with higher oxygen demands, as well as increased caloric input and processing. Higher caloric input is possible in mammals because of the precise occlusion of our dentition, which in turn, is possible because of the novel configuration of the mammalian jaw joint and the initially edentulous state of mammalian neonates (Luo, 2001).

The relative position of the airway to the digestive systems in mammals (Fig. 1) is a hold-over from a general vertebrate configuration (Hildebrand and Goslow, 2001). Swallowed food or liquid must cross

FIGURE 1. INFANT OROPHARYNGEAL ANATOMY.

This diagram of an infant pig is representative of the patterns of morphology in nearly all infant mammals, including humans. Note the relative position of the tongue, oropharynx, larynx and epiglottis.

the opening to the airway. This is a problem for mammals, because, unlike many ectotherms (cold-blooded animals), continuous respiration is a necessity. The need for airway protection, as well as the manipulation and processing of higher nutrient levels, has resulted in a reorganization of the pharynx and oral cavity (Smith, 1992).

Infant mammalian oropharyngeal anatomy is relatively constant across all mammals (Fig. 1, Smith, 1992). The general organization is as follows: the epiglottis contacts soft palate, the tongue is entirely within oral cavity, and the larynx is locked into nasopharynx. While a larger brain is evident in infant primates, the basic relationships among these anatomic structures with respect to feeding holds even for evolutionarily distant

mammals, such as marsupials (German and Crompton, 2000). Although in adult humans, the descent of the larynx distinguishes humans from other mammals, in infants, the anatomy, with respect to feeding is sufficiently similar that other mammals may be used as a model for human function (Crelin, 1987, German and Crompton, 1998).

INFANT FEEDING IN MAMMALS

The basic mechanism of infant feeding has been described for several species (Schwenk, 2000). In general, the tongue functions as a pump, first sucking milk from the nipple into the oral cavity (German and Crompton, 2000). The milk is held inside

the oral cavity and sealed by the tongue/soft palate junction posteriorly. To move the milk back to the valleculae, at the base of the tongue, the seal is broken, and the tongue in the oral cavity rises and pushes the milk into the area underneath the soft palate, but anterior to the laryngeal opening. Milk is moved out of this space, again by action of the tongue. This phase of swallowing has different names: the oral phase of the

swallow, or intraoral transport culminating in vallecular filling.

Milk is moved out of this space, again by action of the tongue in the next phase of movement, which is often called “the true swallow” or the pharyngeal swallow (Jones, 2003). It is the movement of the milk out of the valleculae, past the laryngeal opening, and into the esophagus.

FIGURE 2. NORMAL FEEDING BEHAVIOR.

Feeding is a complex behavior that includes many steps. Input stimuli cause sensory nerves to convey information to the CNS, which integrates this information before sending motor messages back to the peripheral nervous system. The motor patterns produce movement, or kinematics, of the hard and soft tissue structures responsible for observable behavior.

This movement can take two pathways, relative to the laryngeal opening and epiglottal cartilage (German et al., 1998). One, occurring earlier in ontogeny, is around the opening. The epiglottis functions as a "splash guard", but the larynx is not occluded. The other, which occurs later in development, but prior to weaning, is over the opening, that is protected by the bent or flipped epiglottis (Larson and Herring, 1996). As infants grow, they can use both mechanisms prior to weaning, but the change from one to the other occurs before weaning (Crompton et al., 1997).

WHY DO ANIMAL RESEARCH?

Animal research has great potential for helping clinicians in their practice. Normal data are not available or obtainable for many aspects of human function. Radiographic data is difficult to collect in humans (Jones, 2003) because of the health hazards of radiation. Experimental manipulation of humans is often not possible, or the manipulations that make quantification of behavior possible (such as markers to identify structures in radiographic films) are not compatible with human subjects. However, such quantification gives more precise information on normal function, which is essential for the understanding of how pathology disrupt growth and for producing a target for the return of 'normal' function. Understanding deviation from normal is only possible when normal is known.

Normal feeding behavior is a complex loop of interactions (Fig. 2). Sensory input in the form of food consistency, wet/dry, flavor, and volume or amount is the first step. This input is processed in the central nervous system (CNS), where it is assessed, and decisions about subsequent behavior are made. The CNS also provides coordination among the activity of the various pre-motor and motor neurones generating the output to the peripheral nervous system. The motor output is in the form of signals sent to specific muscles, which fire in a highly coordinated temporal pattern. This motor pattern causes a measurable behavior: movement of structures, including tongue,

jaws, soft palate, pharyngeal walls and laryngeal structures. These movements, as well as changes in the physical structure of the food item, are then detected and information on them sent back to the CNS so influencing the next cycle of movement of the feeding behavior.

Dysfunction can occur as the result of disruption of any link in this cycle. A researcher can systematically and predictably disrupt these links, and measure the impact of variation at a specific step in the cycle on the subsequent behavior, and subsequent cycles. My research group has specifically looked at the role that variation in input stimuli has on different behaviors.

RESEARCH QUESTIONS ABOUT INFANT FEEDING

Normal infants willingly suckle when presented with a nipple and milk. But what are the stimuli that initiate this behavior? How does changing those stimuli impact on suckling? These are general questions; more specific questions are required to fully comprehend aspects of suckling not currently understood.

The first step was an investigation into the normal rhythmic behavior of suckling. What elicits rhythmic suckling? Several alternatives were identified: physical stimulus to lips/oral cavity, the presence of milk, a chemo-sensory or a liquid stimulation or rhythmic delivery of the milk. Then another aspect of behavior was examined: what elicits a swallow? Once again, several alternatives were identified: the volume of the aliquot, the frequency of aliquot delivery or the volume of milk that could be held in the valleculae. Each of these factors was varied, and the impact of this variation on the behavior of the infant was measured.

RESEARCH DESIGN

Infant miniature pigs (*Sus scrofa*) were used in this work. Infant pigs are similar in size to infant humans, and are robust research animals, in that they are eager feeders. We

TABLE 1.
RESEARCH DESIGN FOR VARIATION IN INPUT SENSATION DURING
INFANT FEEDING.

A. Variation in delivery frequencies		
<u>Milk Delivery</u>	<u>Duration of Delivery</u>	<u>Different Rates (Hz).</u>
no milk	2-5 seconds	none
long interval/intermittent	20-40 seconds	2.0, 2.5, 3.0, 4.0, 5.6
short interval	until satiation	0.20, 0.25, 0.30, 0.40, 0.56
demand feeding:	until satiation	animal determined rate
B. Variation in delivery volume and frequency		
<u>Milk Delivery</u>	<u>Volume per Aliquot (ml)</u>	<u>Delivery Frequency (Hz)/Period</u>
<u>(ms)</u>		
	Volume Variation	
	0.44	2.5/400 ms
	0.88	2.5/400 ms
	1.76	2.5/400 ms
	Frequency Variation	
	0.44	5.0 Hz / 200 ms
	0.44	2.5 Hz / 400 ms
	0.44	1.0 Hz / 1000 ms
	0.44	0.5 Hz / 2000 ms

designed an automated mechanical feeding system, in order to control the volume and frequency of milk delivery to the infants. This system consisted of a series of pumps that delivered milk, through tubing to an artificial pig nipple. Animals were easily trained to feed unrestrained. We had the ability to independently set the amount and rate of milk delivered. The system is acoustically and electromagnetically quiet, capable of regular disinfection, and works via a length of tubing so that the pumps were located a few meters from the animals.

While feeding, each animal was recorded using digital videoradiography (Siemens Tridoros 150G3 cineradiographic apparatus and a Sony DCR-VX1000 digital video camera). The Siemens system image intensifier is capable of imaging soft tissue

and can magnify up to 2.2 times life. These images were used to determine when a swallow occurred.

To determine the impact of input variation, we first recorded normal behavior. For such scientific experiments, it is important to quantify this behavior. While some differences may be obvious and qualitative, such as sucking or not sucking, others may be quantitative, such as the amount of milk obtained. Next the sensory input to infant pigs was varied in several ways. One set of experiments tested whether mechanical stimulation, chemosensory or liquid stimulation, or the number of "events" stimulation determined normal behavior.

Another set of experiments tested the impact of varying the volume and delivery frequency of aliquots of milk, two inputs for normal swallowing. Both sets of experiments depended heavily on our mechanical milk delivery system. This allowed the precise measurement of the timing of delivery of milk, the volume and frequency of milk delivery. It also allowed the systematic variation of these parameters.

In the first set of experiments, the following scheme was used to test sensory input to suckling: no milk, infrequent delivery (0.2-0.5 Hz, or a delivery of milk every 5 to 2 seconds), frequent delivery (2.0 – 5.0 Hz, or a delivery of milk every .5 to .2 seconds), shown in Table 1A. Different rates of infrequent delivery were used, and then different rates of frequent delivery to test if the specific rate made a difference. From the visual data and pressure recordings in

the teat, calculations were obtained of the frequency of sucking, and, hence, the rhythmicity of suckling. Five replicates of each specific delivery rate were recorded.

In the second set of experiments, we varied the volume of the aliquot, and the frequency of delivery. The combinations used are in Table 1B. The following information was recorded: the time of the delivery pulse, the time of jaw movement (acquisition and transport of milk), and the time of the swallow. From these measured variables an additional fourth was calculated: the total volume of milk per swallow. There were two ages of animals in some replications of this study. Some were younger (pre-weaning) and some were older (near to weaning), but neither group was capable of eating solid food. There was a difference in size that could impact on the volume of the swallow, so where possible, we separated these data.

TABLE 2.
SUCKLING FREQUENCIES FOR DEMAND AND PRESET RATE DELIVERY
(FREQ), STANDARD DEVIATIONS (SD) AND NUMBER OF SECONDS (N)

Pig1	Pig2			Pig2					
	Freq	sd	N	Freq	sd	N	Freq	sd	N
Demand feeding	3.5	1.0	103	4.4	1.2	61	3.5	.7	139
Preset long interval delivery (Hz)									
5.6	4.3	.9	24	4.6	.3	16	4.9	.4	15
4.0	4.6	.4	21	4.8	.3	15	4.4	.9	20
3.0	3.8	.4	20	4.9	.3	23	5.0	.6	19
2.5	4.9	.2	33	4.7	.5	50	4.3	.3	46
2.0	3.5	.4	32	5.0	.4	22	4.6	.5	28
Mean response	4.22				4.80			4.64	
Preset short interval Delivery (Hz)									
0.56	3.6	.1	27	4.7	.7	24	3.4	.1	7
0.40	4.0	.3	82	4.2	.5	110	3.5	.5	47
0.30	3.9	.3	43	4.5	.5	52	3.3	.2	47
0.25	4.1	.2	91	4.1	.2	173	3.7	.4	130
0.20	3.9	.2	52	4.1	.4	42	3.3	.3	35
Mean response		3.90				4.32			3.44

RESULTS

General Behavior

The general behavior of animals was consistent for all feeding schemes. Animals would willingly feed without being restrained. They would walk up to the nipple, and take it in their mouth. An animal would feed for 30–300 sec, providing adequate milk was delivered. After this, animals appeared satiated and usually appeared to play with the nipple, although little feeding occurred. During a suckling sequence, animals occasionally broke off suckling for 200–800 msec, without relinquishing hold of the nipple. Such interruptions defined subsections, which varied irregularly from 2 to 23 sec duration, within the overall suckling sequence. Swallows, defined by the presence of milk in the piriform recesses on cineradiographs, did not occur during these breaks. In general, swallows occurred every two to three cycles. Cycles containing swallows were not statistically different in length from cycles without swallows, as determined from frame counts in cineradiographic films (German et al, 1997). The films confirmed several other

characteristics of feeding that our research group has previously described (German et al., 1992). The animals used tongue movement to acquire and move liquid, and that jaw closure produced compression of the teat by the tongue, and in turn, caused an increase in teat pressure. There was a strong correlation between the time at which the jaw gape reached its minimum and the time when recorded teat pressure reached a maximum ($R^2 > 0.95$). The pressure within the teat was consequently used as a measure of rhythmic oral movement and as a trigger for milk delivery in demand feeding.

Demand feeding, where the animal itself determined the rate of milk delivery, was recorded separately from other trials, to ensure that the animal had not been conditioned to feed at rates determined by other factors (such as stimulus to release milk). It was determined that suckling frequencies were in the range of 3.5–4.4 Hz (Table 2), corresponding to cycle lengths in the range 227–286 msec. Some data suggest that each animal had a preferred frequency that was different from the other animals ($p < 0.001$).

FIGURE 3. ANIMAL RESPONSE TO VARIATION IN MILK DELIVERY TIMING.

A) No delivery produced no rhythmic response. B) The first drop of milk elicited a rhythmic response. C) Intermittent delivery produced a response higher than the preferred rate did. D) Any delivery rate near the preferred rate caused normal behavior.

Response to stimuli to initiate suckling

All animals had a consistent response to the preset, three-stage milk delivery design of no milk, long interval delivery, short interval delivery (Fig. 3). When no milk was delivered, there was no overt rhythmic response from any animal. Behaviorally, the infants were excited, mouthed the teat vigorously, and sometimes seemed to attack it. However, on one occasion a single drip of milk inadvertently left on the end of the teat was sufficient to elicit rhythmic activity lasting several seconds; this sequence was excluded from analysis.

The delivery of the first aliquot of milk greatly reduced the animal's display of excitement, as well as eliciting obvious rhythmic jaw movement. This change in behavior usually occurred in less than 1 sec after the first drop of milk entered the oral cavity. Once the rhythm was initiated, the patterns of jaw movement and of teat pressure were regular, even though the milk was delivered only every 2–5 sec (Fig. 3B). Suckling sequences for all rates of long interval delivery (0.20, 0.25, 0.30, 0.40, and 0.56 Hz) were characterized by rhythmic jaw movements, but at a rate characteristic of the individual, not of the delivery.

When milk was delivered automatically at a rate within a few Hz of the animal's preferred frequency (determined by demand feeding on the automated feed delivery system), suckling was regular and rhythmic (Fig. 3C, D). Significant rhythmicity was evident in every sequence. The rate of suckling here was significantly slower ($p < .0001$) than in the long interval delivery. These patterns were consistent over all delivery frequencies for all animals (Table 2).

Response to stimuli to initiate swallowing

The overall pattern was identical for all ages of animals. The difference in size meant that older animals could hold more liquid in their valleculae, but otherwise the qualitative response to variation was the same for both age groups. When volume of delivery per aliquot of milk was varied, there was no difference in suck rate (sucks/sec), or in swallow rate (swallows/sec) ($p > .1$). The volume per swallow did increase, which is

logical as more milk was entering the animal per unit time ($p < 0.0001$, Fig. 4). On the other hand, when the frequency of milk delivery varied (aliquots/sec), the rate of swallowing increased ($p < .001$), as well as the volume of milk per swallow ($p < .001$, Fig. 5).

INTERPRETATIONS OF THE DATA

These data suggest that some aspects of feeding behavior are constant, irrespective of variation in sensory input, while others vary considerably when input conditions are changed. In general, rhythmic feeding behavior depended on sensory input. Physical sensation (an artificial nipple in the mouth) was not sufficient, but either liquid or chemosensory input (a single drop of milk) was. However, these results suggest a finer scale tuning of normal response. While a single drop of liquid does elicit rhythmic tongue and suckling behavior, it was at a rate higher than normal. Regular delivery of milk was necessary for normal rates of suckling. Thus the animals responded differently to different sensory inputs. However, there were aspects of rhythmic suckling that were impervious to variation. Changes in delivery rate over the range of 1 to 5 Hz did not affect the animal's suckling rate. Thus, animals' sucking behavior would sometimes be entirely out of phase with milk delivery, and there was no sign of any accommodation to this problem. We conclude that while rhythmic suckling can be elicited by specific stimuli, the rate of that rhythm cannot be entrained.

The other set of results indicated that some stimuli produced reflex changes in swallowing behavior while other changes were simple, physically predictable consequences of volume changes. An increase in the volume of milk presented, through larger delivery aliquots, did not change the rate of sucking, the rate of transport of milk, or the swallow rate. This means that, following changes in aliquot volume, swallows could be triggered by differing volumes of milk. Changing delivery frequency, however, changed both the volume of the swallow and the swallow frequency. This is interesting because

FIGURE 4. VARIATION IN SUCK AND SWALLOW RATE WITH VARIATION IN DELIVERY VOLUME.

Neither sucking rate nor swallowing rate changed with variation in delivery volume. Differences due to age are directly attributable to variation in valleculae size. The first panel shows that suck rate was constant over delivery volume. In the second panel, swallow rate was constant with delivery volume. Finally, in the third panel, the volume per swallow increased as delivery volume increased.

FIGURE 5. VARIATION IN SUCK AND SWALLOW RATE WITH VARIATION IN DELIVERY FREQUENCY.

Both sucking rate and swallowing rate changed with variation in delivery rate. The younger animals are pre-weaning, and the older are getting close to weaning age, but have not yet started eating solid food. The first panel shows that suck rate was constant with changes in delivery frequency. However, in the second panel, swallow rate increased with an increase in delivery frequency. In the third panel, the volume per swallow increases as delivery frequency increases.

changing the delivery frequency impacts only on the oral region, which is supplied mainly by branches of Cranial Nerve V, the trigeminal nerve. Sensation in the valleculae, where swallowing occurs, is due to Cranial Nerves IX and X, the Glossopharyngeal and the Vagus. This demonstrates that feeding behavior is not just simple sensory input translating into motor output. There is clearly a higher level of integrating signals that govern this pattern of variation in swallow rate.

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