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Central pattern generation involved in oral and respiratory control for feeding in the term infant

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Abstract

Purpose of review—Drinking and eating are essential skills for survival and benefit from the coordination of several pattern generating networks and their musculoskeletal effectors to achieve safe swallows. Oral-pharyngo-esophageal motility develops during infancy and early childhood, and is influenced by various factors, including neuromuscular maturation, dietary and postural habits, arousal state, ongoing illnesses, congenital anomalies, and the effects of medical or surgical interventions. Gastroesophageal reflux is frequent in neonates and infants, and its role in neonatal morbidity including dysphagia, chronic lung disease, or apparent life-threatening events is not well understood. This review highlights recent studies aimed at understanding the development of oral feeding skills, and cross-system interactions among the brainstem, spinal, and cerebral networks involved in feeding.

Recent Findings—Functional linkages between suck-swallow and swallow-respiration manifest transitional forms during late gestation through the first year of life which can be delayed or modified by sensory experience and/or disease processes. Relevant central pattern generator (CPG) networks and their neuromuscular targets attain functional status at different rates, which ultimately influences cross-system CPG interactions. Entrainment of trigeminal primary afferents accelerates pattern genesis for the suck CPG and transition-to-oral feed in the RDS preterm infant.

Summary—The genesis of within-system CPG control for rate and amplitude scaling matures differentially for suck, mastication, swallow, and respiration. Cross-system interactions among these CPGs represent targets of opportunity for new interventions which optimize experience-dependent mechanisms to promote safe swallows among newborn and pediatric patients.

Keywords

Non-nutritive suck; nutritive suck; swallow; respiration; central pattern generation; preterm; infant; apnea; bolus; brainstem

Introduction

In the mature organism, the processing of ingested food and liquid material occurs in a seemingly stereotyped manner. Upon closer inspection, the dynamics of feeding reveal enormous complexity and coordination among at least 26 pairs of muscles and 5 cranial nerve systems, including trigeminal, facial, glossopharyngeal, vagus, hypoglossal, and the cervical and thoracic spinal cord segments involved in chest wall movements for coordination of respiration with feeding [1,2]. The central patterning of aeroingestive behaviors include

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volitional and reflexive control mechanisms, and benefit from sensory feedback to modify the spatiotemporal organization of the feed sequence to ensure safe swallow [3–5]. Variation in bolus type (liquid or solid), hardness, homogeneity, volume, viscosity, texture, moisture content, and other sensory characteristics of the bolus (taste) serve to modulate the timing and patterning of motor components which constitute the overall feed sequence.

Central pattern generation for suck, lick, mastication, swallow, respiration

Central pattern generators (CPGs) are primarily composed of adaptive networks of interneurons that activate groups of motor neurons to generate task-specific motor patterns [6]. CPGs modulate cycle duration and the duration and intensity of motoneuron bursts in response to CNS and sensory inputs [7]. The development of an *in vitro* isolated mammalian brainstem preparation [8] was essential for the study of the perinatal rhythmical motor patterns in cranial nerves. In the resting state, rhythmical respiratory activity can be recorded from trigeminal (V), facial (VII) and hypoglossal (XII) motoneurons of neonatal rats [8,9], but a second much faster rhythm appears if the glutamate agonist N-methy-D,L-aspartate (NMDA) is added to the bath, with or without other neurotransmitters or their antagonists [8–13]. Since all neonatal mammals begin to feed on milk, it is presumed that the rhythmic non-respiratory oromotor patterns are related to suckling. Indeed, mastication is not seen in young rats before P12 [14].

The isolated sections of the brainstem of neonates containing the cranial V, VII and XII motor nuclei are each capable of generating the sucking rhythm when isolated from the others [15], as are the left and right halves of the trigeminal section [12]. These observations suggest that there could be at least six separate rhythm generators (two V, two VII, two XII) that are coupled together to coordinate suckling during late gestation and infancy. Exactly how these are coordinated, and whether they all persist into adulthood is not known. However, it is possible that the caudal pair is dominant by birth, because the V pair is tonically inhibited by the caudal brainstem [12]. As shown in Figure 1 [16], CPGs are also modulated by descending inputs from the “sucking area” of the motor cortex [17,18].

The gross licking motor pattern is controlled by a brainstem CPG distributed within several subdivisions of the medullary reticular formation (RF) [19]. Descending inputs from cerebral cortex and forebrain to the lick CPG project to widely distributed targets of both the medial and lateral reticular formation. Most projections originating from brainstem orosensory nuclei terminate within the lateral reticular formation. Pre-oromotor neurons appear concentrated in the intermediate zone of the reticular formation and receive convergent inputs from the lateral and medial RF sites to control lick [2]. Sensory feedback from intraoral gustatory and somatosensory afferents modulate the motor pattern for lick, suck, mastication and swallow.

The transition from suckling to chewing occurs gradually over a period that can vary enormously between species. In rats, the first masticatory movements appear around post-natal (P) day 12, and the adult patternis established between P18–21 [14]. Human infants begin to chew after several months, and mastication continues to evolve until the secondary dentition is in place. Mastication and suckling both involve jaw opening and closing, but the power stroke for the suction phase is provided by the jaw depressors during suckling and by the elevators during mastication. Nutritive suckling also includes an expression phase that typically lags the suction phase by 100 milliseconds or more. This involves a stripping ‘peristaltic’ motion of the tongue tip along the length of the nipple or teat and requires activation of the intrinsic tongue muscles via the hypoglossal nerve [20,21]. Clearly, many motoneurons are active during all of the oromotor patterns, but it is unclear if the sucking CPG evolves to eventually control mastication, or if the mastication CPG emerges separately during the weaning period. There is evidence that some neurons located in the antero-dorsal region of the trigeminal principal sensory nucleus (NVsnpr) may form the core of the masticatory CPG in

rats undergo a rapid maturation during weaning and eventually exhibit pacemaker properties [22].

The essential components of the masticatory CPG are found between the rostral poles of the Vth and VIIth motor nuclei, and each hemisection side can generate a rhythm, although they are normally synchronized by commissural axons [16,23,24]. Many neurons among several nuclei in this region project to V motoneurons, but also to the VII and XII nuclei, and they are strongly and reciprocally interconnected [25–27]. Furthermore, many of them fire bursts during fictive mastication in phase with either the jaw closing or jaw opening motoneurons [28,29]. The majority of these 'masticatory' neurons are activated at very short latency from the masticatory area of sensorimotor cortex, and by sensory inputs.

Mastication patterns vary greatly between foods, and change systematically during a chewing sequence based on sensory feedback. Unlike locomotion, rhythmic orofacial movements including the basic patterns of mastication are represented in the cerebral cortex. Coordinated movements of the jaw, tongue, lips and cheeks can be evoked in anesthetized animals by repetitive electrical stimulation of a large region of the sensorimotor cortex, and other forebrain and midbrain structures. Some of these movements, which strongly resemble natural mastication, including different patterns such as incisal gnawing and left and right molar chewing are represented at specific cortical sites [30]. For example, in rabbit, small rapid vertical movements powered by the digastrics (sucking) are located rostrally; vertical mastication behind these, and patterns with strong lateral swings in the postero-lateral zone of the "masticatory" cortex [30].

Interneurons, which have been identified in the brainstem, are capable of generating a basic swallow pattern in the absence of peripheral or descending cortical inputs [31]. Swallowing is observable in the developing fetus by the 11^{th} week of gestation which is essential for the regulation of amniotic fluid [32]. Swallowing skills develop progressively during fetal and neonatal maturation [33]. At birth, the neonate must transition from swallowing in a liquid environment to integrating swallowing with airway-protective mechanisms. McFarland and Tremblay [31] emphasized that sensory experience is crucial to optimize pattern formation and brain development during the presumed critical period for attainment of swallowing proficiency. Driving intraoral and pharyngeal sensory afferents mediated by the trigeminal and glossopharyngeal system during suck can initiate or modulate a swallow [4,34].

Functional imaging in mature systems has revealed that swallowing is controlled through a network of cortical areas that is considerably more distributed than previously thought, and this network shares loci with other ororhythmic movements including speech. For example, an extensive network of overlapping and distinct BOLD activations for tongue movements and swallowing, including SMA, anterior cingulated area, Brodmann's areas 3 and 4, cuneus, precuneus, supramarginal gyrus, and cerebellum have been observed [35]. A subsequent meta-analysis, based on 10 published studies and a total of 121 subjects, resulted in the identification of distributed and partly overlapping cortical networks involved in the sensorimotor control of water and saliva swallowing [36]. A between-condition meta-analysis revealed clusters with higher activation likelihood for water than saliva swallowing in the right inferior parietal lobule, right postcentral gyrus, and right anterior insula. Voxel clusters with higher activation likelihood for saliva than for water swallows were found in the bilateral SMA, bilateral ACG, and bilateral precentral gyrus. Therefore, swallowing is not a simple reflex, but rather a complex coordinated sensorimotor process generated by multiple levels of neural control distributed among several physiological systems [31]. The swallowing network is adaptive and subject to modification by experience-dependent plasticity [37].

Whole-cell patch-clamp recording techniques were used to study the isolated respiratory pattern generator located in the pre-Bötzinger complex (pre-BötC) of the ventrolateral medulla in rats [38–41]. Spatially distributed populations of interneurons, premotoneurons (preMNs), and motoneurons (MNs) in the brainstem and spinal cord serve distinct functional roles in mammalian respiration [42]. Interacting populations of interneurons generate temporal features of the motor pattern including network rhythms, preMNs (defined as cells with axonal connections to MNs) function as pattern formation elements and substrates for rhythmic drive transmission, whereas MNs generate motor output. Inspiratory rhythm, generated by interneurons in the pre-BötC of the ventrolateral medulla [39,43,44], propagates through preMN transmission circuits to spinal and cranial MNs.

Drinking, eating, swallowing, and breathing are tightly coupled motor behaviors, with swallowing dominant to respiration in normal individuals [31,45,46]. Swallowing always interrupts the breathing of infants and children [45,47–49]. The cessation or interruption of respiration during swallowing is known as *swallowing apnea* and is duein part to the closure of the airway and neural suppression of the respiratory pattern generator in the brainstem [45]. Breathing-swallowing coordination is defined by the point in the respiratory phase cycle where swallowing apnea occurs [49]. Swallowing usually begins during the expiratory phase of breathing when drinking. In adults, approximately 75–95% of swallows are initiated during the expiratory phase [46,50] compared to just 39% in newborns [51]. The pause in respiration continues for 0.5 to 1.5 seconds to accommodate the swallow, and respiration resumes with an expiratory cycle to help prevent aspiration of residual food in the pharynx post-swallow [52, 53]. Conversely, respiration can resume with an inspiratory cycle when performing sequential swallows while drinking from a cup [54]. The respiratory rhythm is also perturbed during the onset of mastication, with respiratory cycle duration decreased during mastication but increased during swallowing. The ‘exhale-swallow-exhale’ sequence is manifest during eating.

Term infants through the first year of life

Nutritive swallows of healthy term infants occur predominantly at the inspiratory-expiratory cusp, followed by mid-expiration, and occasionally at the expiratory-inspiratory transition [51,55,56]. Infants whose swallow-respiration coordination during feeding deviates from this pattern could be considered ‘disordered.’ For instance, premature infants (33 weeks post-conception), unlike full term infants, swallow predominantly during respiratory pauses [57]. Recently, the maturation of breathing-swallowing coordination was examined during feeding in ten healthy term human infants through the first year of life [48]. More than 15,000 swallows were sampled across ten assessments between 48 hours and 12 months of age. Mid-expiratory swallows represented the dominant pattern of breathing-swallowing coordination within the first 48 h (mean = 45.4%), but the prevalence of this pattern declined rapidly in the first week to 29.1%. Inspiratory-expiratory swallows increased significantly with age, particularly between 9 months (37.0%) and 12 months (50.4%). Nearly 75% of swallows were followed by expiration in the latter 6 months, which is an adult-like characteristic. Post-swallow expiration is a robust feature of breathing-swallowing coordination from birth, with two major shifts in the precise patterns occurring (1)after 1 week of postnatal feeding experience, and (2) between 6 and 12 months, attributed to neural and anatomical maturation [48].

The coordination of nutritive and non-nutritive swallowing with breathing was assessed longitudinally in 10 healthy term infants from birth to 1 year of age [49]. Swallows were classified into five respiratory-phase categories, including mid-inspiration (II), mid-expiration (EE), inspiratory-expiratory cusp (IE), expiratory-inspiratory cusp (EI), and mid-pause (P). Breathing-swallowing coordination differed markedly between the two swallowing conditions, especially between 2 weeks and 2 months. Significant condition effects were found in up to four respiratory-phase categories (II, IE, EI, and P). The condition effect was minimal from 9

months with only IE swallow proportions differing between conditions. A '*critical period*' is implicated for the genesis and modulation of the neural response to oropharyngeal stimulation during feeding. Interruption of this developmental process may significantly impact infants with neurological and/or respiratory disorders and requires further investigation.

The impact of bolus ingestion and level of consciousness on swallowing apnea duration (SAD) was studied in 10 healthy term infants [58]. SAD during wakefulness, sleep, and feeding (breast or bottle) was measured 10 times from birth to 1 year of age. Based on 19,402 swallows, SAD during feeding was significantly shorter than SAD of non-nutritive swallowing (during wakefulness and sleep) regardless of age. SAD did not change significantly within the first year of life in any of the three conditions and there was no change in the relative durations of nutritive, wake and sleep conditions with age. The absence of an age effect suggests that the neural mechanisms controlling SAD are fundamentally brainstem-mediated and largely determined at birth in healthy term neonates.

Given the known decrease in global cerebral activity during sleep, the sleep-wake paradigm was used to elucidate suprabulbar influences [59]. Non-nutritive breathing-swallow control (BSC)of 10 healthy human infants was monitored longitudinally during wakefulness and sleep from birth to 1 year of age. Digitized recordings of submental muscle activity, nasal airflow, and thyroid acoustics enabled the categorization of swallows as a function of respiratory phase. In contrast to the change in the overall pattern of BSC with age, and despite postnatal cortical proliferation and development over this time, no arousal-related differences were observed during the first year of life. Thus, the non-nutritive BSC in infants appears to be under complete brainstem control.

Advanced swallow assessment technologies

The use of microphones permit detection of swallow sounds in adults [60] and infants [55, 61,62]. Cervical auscultation (CA) utilizing an accelerometer placed over an infant's throat was developed to include more objective, quantitative parameters that are reproducible among clinical populations to evaluate dysphagia in adults, children, and infants [63,64]. CA was performed recently with an accelerometer and microphone to describe the stability of initial discrete swallow-associated sounds (IDS) of adult and infant feeding [65]. A variance index (VI) was calculated to quantify the stability of IDS. The VI of adults swallowing liquid did not differ from that of preterm infants older than 36 weeks PMA, but was lower than the VI of preterm infants younger than 36 weeks PMA. The authors suggest that stability measurements of swallow-associated sounds may provide a biomarker for neurologic integrity.

Motor evoked potentials (MEPs) recorded from pharyngeal and anterior hyomandibular (submental) muscles at rest have been used to evaluate treatment effects on neural pathways underlying swallowing. A recent study documents a novel method for recording reliable intra- and inter-session MEPs at the submental muscle group during task-related volitional swallowing [66]. MEPs were elicited by single-pulse transcranial magnetic stimulation (TMS), triggered when a pre-set threshold of surface electromyographic activity was attained. Results indicate that surface electromyography-triggered TMS allows reliable measurement of MEP amplitude at the submental muscle group within and across sessions when muscles are pre-activated during volitional swallowing. This methodology will be useful for future investigations on the effects of pathology and modulation of the neural network for swallowing.

A promising approach to the study of pharyngoesophageal motility in infants and children involves the application of pharyngo-UES-esophageal micromanometry [3,5,67–72]. The micromanometric method has been validated and new applications developed to measure the reflexes of interest pertinent to swallowing and primary peristalsis. Recently, Jadcherla and colleagues have defined the maturational changes in enteric nervous system and quantified

related motility measures in premature infants. Pharyngeal-upper esophageal sphincter-esophageal body motility characteristics were defined across maturation during infancy. Additionally, this work included a characterization of the sensory motor aspects of the vago-vagal reflex modulation during peristalsis. Pharyngeal reflexive swallowing (PRS) is more frequent than pharyngo-UES-contractile reflex(PUCR). Each reflex type manifests distinctive characteristics in air and water stimuli, and both PRS and PUCR have implications for the evaluation of swallowing in infants [72].

Entrainment of oromotor CPGs to promote the transition to oral feed

Sensorimotor entrainment as a habilitation strategy(i.e., utilizing natural mechanical stimulation, or other modality such as olfactory, vestibular, acoustic), has ecological validity in assisting the infant to produce functional ororhythmic behavior and enhance the transition to oral feeding. This approach is consistent with contemporary ideas on the role of sensory-driven neural activity and critical periods [73,74] during late gestation and early infancy in the formation of functional ororhythmic and deglutition networks. Use of a mechanical entrainment stimulus also has the distinct advantage of being safe, pleasurable, and salient to developing brainstem ororhythmic CPGs [75,76].

Altering the stiffness of the pacifier is also effective in reorganizing the ‘burst-pause’ structure of the NNS CPG in neonates [77]. Infants who were born prematurely were offered the Soothie™ and SuperSoothie™ silicone pacifiers at their3-month follow-up clinical evaluation of feeding skills, health, and development. Even though bulb and cylinder displacement volume and surface geometry of these two widely used pacifiers are virtually identical, their mechanical stiffness profiles differ by a factor of 7x due to the increased wall thickness of the SuperSoothie™ pacifier. The elevated mechanical impedance of the SuperSoothie™ presents a significant challenge to infants and resulted in shorter NNS bursts, reduced numbers of NNS bursts, and modified suck cycle frequency within-burst. These observations provide additional evidence of the sensitivity of the suck CPG to changes in local environment.

Conclusion

Information threads from neuroscience, neonatology, gastroenterology, pediatrics, pulmonary physiology, developmental speech physiology, speech pathology, and medical physics are converging rapidly on the mechanisms underlying the development of aeroingestive functions and the highly adaptive and distributed cortical and brainstem neural networks responsible for central pattern generation. These multidisciplinary information streams will enhance our understanding of cross-system interactions, plasticity, adaptive control, and issues related to neurodevelopmental outcomes, which in turn will facilitate new methods of assessment and novel entrainment including multimodal stimulus interventions for the prohabilitation of the late gestation infant, or rehabilitation of the child with a feeding disorder.

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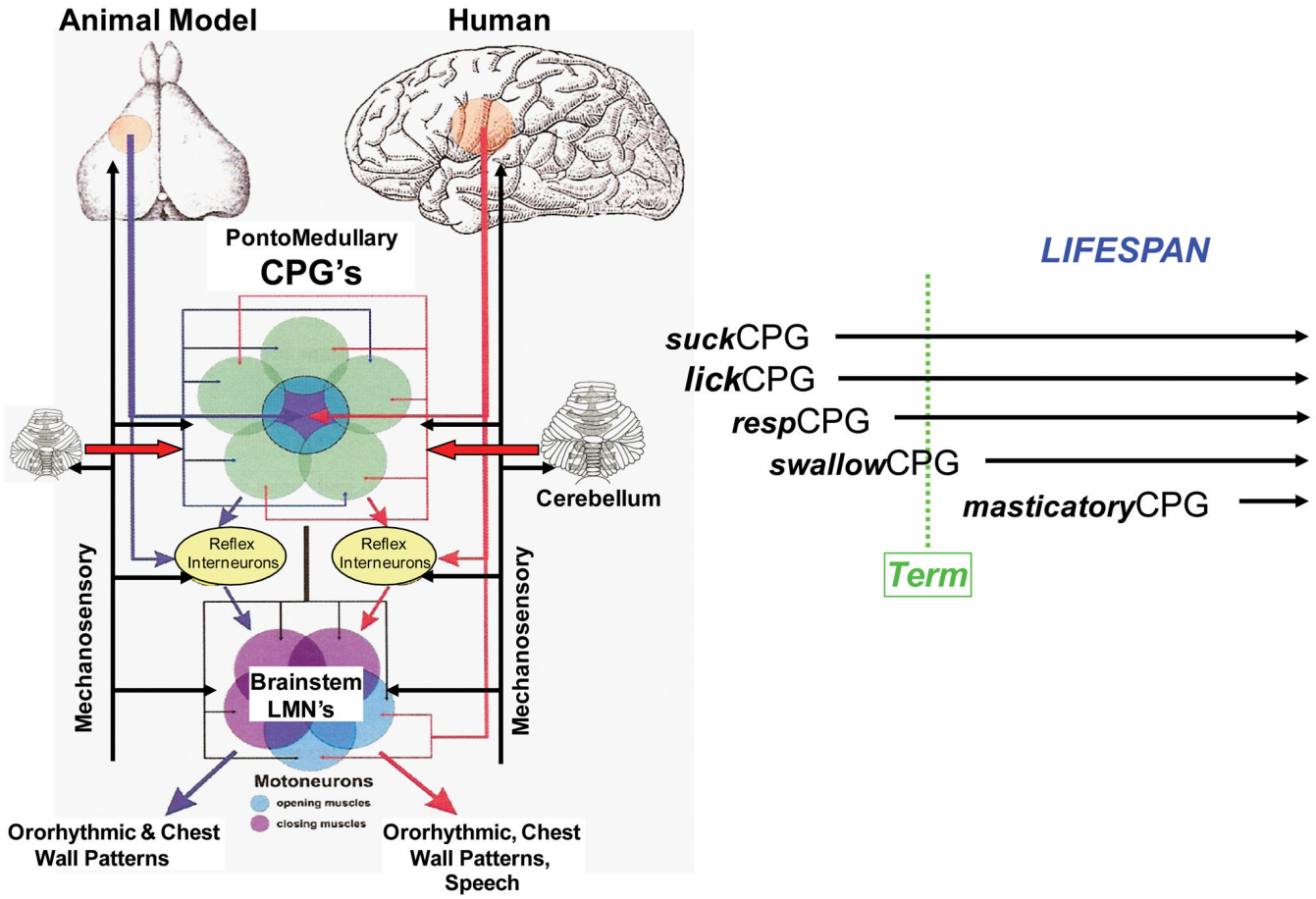

Figure 1.

Ororhythmic central pattern generators. An adaptation of a model proposed by Dr. James Lund and colleagues [16], and extended to include modulatory inputs from the peripheral afferents and the cerebellum.