Published in final edited form as:

Curr Opin Neurobiol. 2014 October ; 0: 94–100. doi:10.1016/j.conb.2014.06.012.

Central pattern generator for vocalization: Is there a vertebrate morphotype?

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Abstract

Animals that generate acoustic signals for social communication are faced with two essential tasks: generate a temporally precise signal and inform the auditory system about the occurrence of one's own sonic signal. Recent studies of sound producing fishes delineate a hindbrain network comprised of anatomically distinct compartments coding equally distinct neurophysiological properties that allow an organism to meet these behavioral demands. A set of neural characters comprising a vocal-sonic central pattern generator (CPG) morphotype is proposed for fishes and tetrapods that shares evolutionary developmental origins with pectoral appendage motor systems.

Acoustic communication behaviors are known for the two major radiations of jawed vertebrates (Gnathostomata), the ray-finned and lobe-finned fishes or Actinopterygii and Sarcopterygii (also includes tetrapods), respectively (Figure 1A,B). As reviewed here, these behaviors in fishes rely on temporally precise (i.e., minimal jitter) and synchronous firing of motoneuron populations to drive acoustic modulations at rates that can exceed 100 Hz [1]. Although the challenges of temporal precision on a millisecond timescale and synchronicity across a pool of interconnected neurons may be widely shared among sonic systems, little is known about the underlying neural mechanisms. An added sensory-motor challenge is the need to distinguish one's own acoustic signal from others originating from external sources [2]. With the goal of defining these and related mechanisms, sound-producing fishes are used as model systems. The studies have two, not mutually exclusive, goals. The first is to identify the neural basis for the temporal patterning of acoustic signal modulations on millisecond timescales, complementing ongoing investigations of the sense of hearing [3]. This includes characterization of the intrinsic and network properties of a hindbrain central pattern generator (CPG) for vocalization. A second goal is to identify a vocal-sonic CPG morphotype, "the characters believed to be present in the common ancestor, based on a determination of shared primitive characters of the stem taxa" [4]. As we speculated earlier [1], can we identify "the anatomical and neurophysiological properties of sonic-vocal networks in fishes found in the sonic-vocal networks of birds and mammals", in an attempt

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to “reconstruct” how the complex vocal phenotypes of birds and mammals were “built over evolutionary time” [5]?

Vocal fish as model systems

Sound production among actinopterygian fishes is best known for teleosts, the most species-rich group of vertebrates [6], with reports for more basal actinopterygian groups as well (see [1] for comprehensive review). Among sarcopterygians, sonic species are well documented among all of the major lineages of tetrapods. Sound production in closely related lungfish (Dipnoi) has been noted, but there remains a need for thorough investigations of lungfish and the coelacanth *Latimeria* before we can conclusively state that sonic behavior is a shared primitive character of bony vertebrates (Figure 1B).

We first adopted the term vocal [7] to describe sonic mechanisms in a single order and family of fishes known as toadfishes (Batrachoidiformes, Batrachoididae) that generate sound by rapidly vibrating the swim bladder via the contraction of a single pair of sonic muscles. As noted then, vocal fish share the following characters with sonic tetrapods: (1) social context-dependent acoustic signals, (2) a dedicated sonic organ (swim bladder) analagous to the syrinx and larynx, (3) sonic muscles (syringeal, laryngeal, swim bladder) derived from occipital somites, (4) sonic muscles innervated by occipital nerve roots, homologues of the hypoglossal nerve that innervates syringeal muscles in birds, and (5) consistent with 4, the same central nervous system (CNS) location as the sonic, tracheosyringeal division of the hypoglossal motor nucleus in birds. While acoustic communication may have independently evolved multiple times among teleosts, comparative surveys map the location of vocal premotor and/or motoneurons in distantly related groups to the same region of the caudal hindbrain-rostral spinal cord [8]. Studies of early development show that the vocal premotor-motor circuitry in toadfishes maps to this same CNS compartment, overlapping the site of comparable circuitry in tetrapods [9].

The location of sonic motoneurons among vocal vertebrates has been extensively mapped [review in 9]. A wide range of neurophysiological studies, from electromyography to extracellular recordings from the CNS and nerves driving sonic muscles, suggest that the hindbrain can pattern both the fine and gross temporal properties of vocalizations [review in 10]. Whereas a growing literature continues to show how the cellular and network properties of local brainstem and spinal circuits pattern motor behaviors as divergent as locomotion, eye movement and respiration [11–14], there are few such studies for vocalization (also see Sweeney and Kelley, this issue). For tetrapods, this is due, in part, to strong coupling of vocal with respiratory CPGs that poses significant technical challenges in delineating the neuromuscular patterning of individual syllables and entire calls, and limited surgical accessibility of the hindbrain for recording from vocal CPGs in intact, *in vivo* preparations [e.g., 15–17]. Vocal teleost fish lack these limitations and offer tractable models to identify cellular and network properties of a brainstem circuit that, in this case, leads to a simple translation between hindbrain output and the temporal attributes of vocal behavior.

Hindbrain vocal CPG in fish

Extreme temporal synchrony and precision in high gamma range

The general organization of a brainstem vocal network in fishes resembles that of birds and mammals; hindbrain premotor nuclei are the target of midbrain (periaqueductal gray) neurons activated, in turn, by the preoptic area-anterior hypothalamus [18,19]. Most neurophysiological studies of hindbrain CPG mechanisms for acoustic signaling in teleosts are in toadfishes that, like most fishes, produce pulsatile calls (Figure 2A). Duration, amplitude and pulse repetition rate (PRR) that also sets the fundamental frequency in fish, are directly patterned by a final command signal coming from the vocal motor nucleus (VMN), a population of highly interconnected, homogenous motoneurons [7,20,21]. VMN output is readily recorded as a *fictive call* from vocal occipital nerve roots that innervate the paired sonic muscles, while intracellular recordings can simultaneously monitor the activity of individual motoneurons during fictive calling (Figure 2A, B shows representative records for agonistic grunts). Fictive calls are rapid (~100 Hz at 16° C), oscillatory events comprised of spike-like nerve potentials that arise from the summation of highly synchronous, temporally precise VMN output (Figure 2B) [20,21]. Each fictive nerve spike translates into one sound pulse (Figure 2A). The size-dependent recruitment of motoneurons patterns vocal amplitude, while a set of intrinsic (low excitability, rapid membrane repolarization) and network (dense excitatory and inhibitory inputs, electrotonic coupling) properties ensure population level firing synchrony across VMN at natural call PRR and duration [20].

Two anatomically separate premotor populations within the adjacent reticular formation, the vocal pacemaker (VPN) and vocal prepacemaker (VPP) nuclei, code for vocal PRR and duration, respectively [10,21]. The distinct coding functions of these premotor neurons are determined by their intrinsic properties, namely subthreshold oscillations for VPN and sustained depolarizations for VPP [10]. VPN neurons fire in the high gamma range, a character that is directly translated into VMN firing rate, the contraction rate of superfast sonic muscles, and the PRR of natural vocalizations.

Vocal corollary discharge

A central corollary discharge can account one's ability to distinguish self-vocalization from externally generated acoustic signals [2]. Vocal CPG neurons project to central auditory nuclei, including a hindbrain efferent nucleus that directly innervates the hair cell epithelium of the saccule, the main auditory division of the inner ear in many fishes [10,21]. Auditory efferent (AE) neurons represent a functional analogue, if not homologue, of olivo-cochlear neurons in tetrapods [22]. A recent report in midshipman fish (*Porichthys notatus*) shows the synaptic basis for high fidelity transfer of information from duration coding VPP premotor neurons to AE neurons (Figure 2C, D), the first mapping in a vertebrate of a discrete vocal corollary discharge (VCD) circuit [23]. The more widespread occurrence of a VCD duration code is suggested by extracellular and evoked potential recordings in bats and monkeys (review in [23]) and a recent report indicating a predominant role for call duration and not the respiratory cycle in the patterning of vocalization in rodents [24].

What can fish tell us about tetrapods?

Recent comparative studies suggest the presence of hindbrain premotor neurons in tetrapods with coding properties like those in toadfishes that can pattern transitions in acoustic signals on a millisecond timescale. Superfast sonic muscles, first observed for the toadfish swim bladder and rattlesnake tailshaker [25], have recently been identified in the avian syrinx and bat larynx [26,27], implying the presence of a superfast premotor network like that in toadfishes. Like the vocal occipital nerve volley in fish (Figure 2A), the vocal laryngeal nerve volley in the African clawed frog, *Xenopus laevis*, is a series of synchronous, spike-like events matching the sequence of natural sound pulses [28] (also see Sweeney and Kelley, this issue). Hindbrain neurons in *Xenopus* [29] that pattern a fast PRR (trill) component of the courtship call have the combined coding properties of toadfish VPP and VPN neurons; central recordings suggest comparable mechanisms in terrestrial frogs [30].

The one to one relationship between neural output and sound pulses in fishes and frogs, as well as superfast motor systems in fishes, reptiles, birds, and mammals, may be examples of convergent evolution. However, we propose more broadly that cellular and network properties like those in toadfishes and frogs underlie centrally generated timing signals [sensu 31] providing millisecond precision that coordinate the neuromuscular basis of vocalization irrespective of peripheral musculature (swim bladder, syringeal, laryngeal) mechanics. Studies of songbirds, in particular, are consistent with this point [32]. The ability to rapidly switch between vocalizations with widely divergent temporal characters, for example from a “purring”, toadfish-like mode of pulsatile vocalization to a “flow-driven mode” dependent on the biophysical properties of vibrating membranes [33,34], likely depend on reconfiguration of vocal network output [sensu 35] via mechanisms identified in fishes and frogs.

Are vocal CPGs novel innovations of movement-related networks?

When we first proposed the origins of vocal CPG neurons from a caudal hindbrain compartment [36], we emphasized that inferior olive neurons, an essential player in the temporal patterning of a range of movement behaviors [31], also originate from this same hindbrain region [9, 37]. An explicit link between vocal and locomotor circuits has since been demonstrated in a precise mapping of the neuroepithelium in embryos and larvae of vocal midshipman and non-vocal species of fishes showing that the vocal network compartment also gives rise to pectoral fin motoneurons [38]. This provides essential evidence to support the hypothesis that vocal systems are novel innovations in vertebrate motor control that share origins from other motor systems [36,39,40], in this case the pectoral (fin, forelimb) system shared by both major radiations of jawed vertebrates (Gnathostomata, Figure 1B).

As reviewed elsewhere [1], shared evolutionary developmental origin of vocal and pectoral motor systems is consistent with the well-documented use of pectoral appendages for sonic communication in teleosts, birds and primates (e.g., catfish and manakin, Figure 1A) [e.g., 41–43]. The term vocal-sonic CPG reflects the shared origin of networks dedicated to sound production (vocal) and those (e.g., pectoral) that are multifunctional, including a role in

sound production. Although neurophysiological evidence is lacking, behavioral evidence in midshipman fish shows a strong coupling between vocalization and pectoral rhythmicity, and in mammals between vocalization and pectoral (forelimb)-gestural movements (review in [1]). Shared patterns of forebrain control for vocalization and locomotion [e.g., 40] are consistent with shared evolutionary origins. While pectoral motoneurons shifted from a hindbrain-spinal level in fishes to spinal only locations in tetrapods (forelimb), coincident with decoupling of the pectoral system from the head (Figure 1C) [38], there is evidence for the retention of premotor pattern generating circuitry at hindbrain levels in tetrapods [44].

Is there a vocal-sonic CPG morphotype?

We proposed earlier that caudal segments (rhombomeres) of the developing hindbrain were genetically specified for the premotor circuitry of many rhythmic behaviors, i.e., behaviors that are “repetitive, stereotyped, and have a predictable temporal pattern determined by a network of neurons referred to as either a pacemaker, neural oscillator or central pattern generator” [36]. Expanding upon this proposal, studies of early development support the hypothesis that the same hindbrain-spinal compartment is the source of a premotor-motor network whose output coordinates the activity of sonic muscles underlying vocalization among vertebrates (Figure 1C) [9].

The emphasis here is on premotor neurons that provide timing signals for the activation of one or more muscles that underlie the execution of a motor behavior [31], in this case vocalization. The premotor neurons patterning the activity of these neuromuscular units may share developmental origins from neurotransmitter and transcription factor-defined hindbrain populations comparable to those recently identified in mammals [45] and zebrafish [46,47] (also see Sweeney and Kelley, this issue). These neurons, in turn, may have distinct intrinsic and/or network properties like those being identified in fish and frogs [10,20,23,29] that determine the vocal system’s enhanced temporal precision and synchrony [10,20,48] compared, for example, to motoneuron activity underlying locomotion [e.g., 11,20,49].

In an attempt to “reconstruct” how the vocal phenotypes of bony vertebrates (Figure 1A, B) were “built over evolutionary time” [5], the following suite of neural characters is proposed for a vocal-sonic CPG morphotype, inclusive of both morphological and physiological characters.

1. Developmental origins from a caudal hindbrain-spinal compartment (Figure 1C).
2. Coordinated activity with pectoral premotor circuitry that shares origins from the same CNS compartment (Figure 1C).
3. Temporal precision and synchrony on a millisecond timescale shaped by intrinsic and network properties (Figure 2A–C).
4. Neuronal phenotypes with distinct, genetically specified coding functions (e.g., duration, PRR) (Figure 2B,C).
5. Corollary discharge circuit that codes for call duration (Figure 2D).

6. Direct input from vocal midbrain neurons receiving input, in turn, from the preoptic area-anterior hypothalamus.

Even more broadly, will investigations of insects [e.g., 50,51], which share sonic CPG characters with fishes [2,23], reveal a CPG morphotype shared across the animal kingdom that sculpts the neural basis for acoustic signaling from the chirps of insects to the growls of fish and speech of humans?

Acknowledgments

Research support for the author's work reviewed here is from NIH DC00092 and NSF IOS 1120925. Thanks to M. Brainard and T. Fitch for the invitation to write this essay; to B. Chagnaud for help with the illustrations; to BC, N. Feng and especially I. Ballagh and TF for many helpful comments on the manuscript.

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Highlights

Vocal communication is widespread among teleost fishes, the largest group of vertebrates.

Vocal fish and tetrapods share an evolutionarily conserved hindbrain CPG region.

Vocal CPG of fish has distinct compartments coding for equally distinct temporal properties.

Vocal CPG of fish displays extreme levels of temporal precision on a millisecond timescale.

Vocal CPG shares evolutionary developmental origins with pectoral movement system.

Figure 1.

Vertebrate sonic behaviors and phylogeny. (A) Representative vocalizations of bullfrog (bar scale represents 1 s), zebra finch (250 ms), squirrel monkey (200 ms), midshipman fish (500 ms), catfish (250 ms) and club-winged manakin (100 ms). Vocal (V) and pectoral-sonic (PS) mechanisms indicated. (B) Cladogram showing jawless (Agnatha, e.g., Petromyzontiformes - lamprey) and jawed (Gnathostomata) vertebrate radiations (Osteostracans are an extinct agnathan group with pectoral fins). (C) Schematic in longitudinal plane showing location of vocal and pectoral-sonic (PS) motoneurons. Modified from [1].

Figure 2.

Vocal CPG morphotype. A) Left: Hydrophone records of a repetitive series of agonistic "grunts" (top) and individual grunt (bottom) from the plainfin midshipman fish, *Porichthys notatus*. Right: Vocal nerve volley (top) and single nerve burst (bottom) directly predicts temporal properties of natural calls (left). Grey shading indicates expanded records in bottom panels. B) Fictive calls patterned by extreme synchrony in oscillatory-like, motoneuron activity directly determine natural call properties. Corresponding vocal nerve (top) and intracellular motoneuron (bottom) recordings of a fictive grunt are aligned. Pulse repetition rate (PRR, determines fundamental frequency in fish) and duration (time between first and last pulses) are indicated. Left inset shows motoneuron action potential (black) matched one to one with vocal-nerve spike, i.e., fictive sound pulses (red). C. Durations of sustained depolarization (depol. half width) of auditory efferent (AE) neurons (top left inset) are highly correlated with duration of fictive grunts (lower right inset; color-coded to indicate match with intracellular AE records in top inset). Regression plot shows cumulative results during spontaneous and glutamate evoked (midbrain injections) calls (red, n=5 neurons) or electrically evoked (midbrain stimulation; black, n=10 neurons) calls. D. Summary of vocal corollary discharge pathway identified in midshipman fish. Auditory efferent (AE) neurons directly receive call duration information from the vocal CPG, directly innervate the auditory hair cell epithelium, and generate a vocal corollary discharge

(VCD) that prevents or diminishes the level of responses to auditory refference from self-vocalization. A–D from [23].