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The Mammalian Diving Response: An Enigmatic Reflex to Preserve Life?

W. Michael Panneton
Department of Pharmacological and Physiological Science, St. Louis University School of Medicine, St. Louis, Missouri
pannetwm@slu.edu

The mammalian diving response is a remarkable behavior that overrides basic homeostatic reflexes. It is most studied in large aquatic mammals but is seen in all vertebrates. Pelagic mammals have developed several physiological adaptations to conserve intrinsic oxygen stores, but the apnea, bradycardia, and vasoconstriction is shared with those terrestrial and is neurally mediated. The adaptations of aquatic mammals are reviewed here as well as the neural control of cardiorespiratory physiology during diving in rodents.

The mammalian diving response is an amalgam of three independent reflexes inducing physiological changes that counter normal homeostatic control. This remarkable behavior is called the diving response (DR) since it was first studied in pelagic pinnepeds (106, 108, 215), but all aquatic mammals, including whales and dolphins, posses this response. Moreover, numerous studies have shown that all mammals, including those terrestrial (Panneton WM, unpublished observations), have a DR, from the primitive platypus (10, 112) to humans (73, 132), and can be extended to include all vertebrates (63, 218). For example the common laboratory rat maintains a brisk DR to underwater submersion (67, 159, 185); in our hands, the response is seen in 100% of rats, 100% of the time. The hypothesis that the purpose of the DR is to conserve intrinsic oxygen stores, no matter what the species, appears evident to us.

The DR is based in respiration where the animals are rendered apneic by underwater submersion. The source of the organisms' oxygen–a mammal cannot breathe underwater or it will drown–is lost underwater. Thus, to survive, underwater mammals must rely on intrinsic oxygen stores bound mostly in blood to hemoglobin and in muscle to myoglobin. The conservative use of intrinsic oxygen stores maintains aerobic metabolism; when these stores are depleted, the diving animal has reached its aerobic dive limit (ADL), a metabolic threshold where diving duration goes beyond intrinsic oxygen stores and is marked by lactate concentration in blood increasing above resting levels (22, 118, 124, 200). The cardiovascular system helps remedy this problem of anoxia. A controlled reflex of onset bradycardia, a parasympathetic response, is foremost and reduces cardiac output dramatically, which by itself would induce a precipitous drop in arterial blood pressure. Thus the sympathetic nervous system counteracts the ensuing pressure drop, and a massive peripheral vasoconstriction commences redistributing circulating blood by reducing blood flow in cutaneous, muscular, and splanchnic circulations, but a maintained or augmented flow to the central nervous system and heart (15, 94, 105, 256). Since these reflex behaviors, collectively coined the DR, are found in all vertebrates studied (69, 119), they may be the ultimate weapon organisms posses to maintain life during asphyxia.

This review will cover only the DR of mammals, although birds, especially ducks and penguins, commonly are studied. The pioneering studies on birds by Scholander (215), Folkow (70), Blix (14), Butler and Jones (25), and their colleagues have been reviewed previously (15, 26, 27, 63, 119, 123, 167, 198). It might be noted, however, that the avian responses are somewhat dissimilar to those seen in mammals in that the bradycardia and peripheral vascular responses are slower in onset than those in mammals and may be more the result of slower activation of arterial chemoreceptors rather than the rapid activation of nerves innervating the face.

Adaptations of Aquatic Mammals

Anatomical Adaptations

Several anatomical adaptations that promote diving efficiency are found in seals. Pinnepeds possess an elastic and bulbous ascending aorta (aortic bulb) hypothesized to maintain arterial pressure during the long diastolic intervals during diving bradycardia (53). The high volume of blood usually seen in aquatic mammals also must be shunted somewhere after massive peripheral vasoconstriction. Many seals have developed large venous retes in continuity with the inferior vena cava as well as an extradural intravertebral vein (169) to store such blood. The heads of dolphins also have extensive venous plexi (47), possibly for the same purpose. Many seals also have developed a caval sphincter of striated musculature near the diaphragm to regulate venous return to the heart (64). These anatomical adaptations have been reviewed previously (15, 27, 63).

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Physiological Adaptations

If the rationale behind the DR is to preserve intrinsic oxygen stores (FIGURE 1), it is especially important for diving aquatic mammals, which spend up to 80% of their time submerged (77, 95), to bank as much oxygen as possible. Indeed, diving mammals do this several ways. Oxygen conservation is enhanced by gliding behavior (251) or descent approaches (146) in many diving species. Behavior coordinates with physical adaptations as the animal matures; physiological factors limiting dive duration are correlated with animal size and mass (21, 100, 122). Physiological adaptations (FIGURE 2) of diving animals include increased blood volume and elevated hematocrit, hemoglobin, and myoglobin, whereas oxygen-use rates are minimized via regulation of metabolism, heart rate, and peripheral vasoconstriction (26, 27, 63, 118, 119, 121).

Oxygen Storage

The size of oxygen stores as well as their rate of utilization limits aerobic dive capacity; the mammals that dive for the longest durations have the largest oxygen stores. Bert (15) first noted that diving ducks had a much larger blood volume than barnyard hens, an observation confirmed in several species (128, 177). Indeed, blood volume is at least three times greater in diving mammals. This volume is augmented by the fact that considerably more oxygen is bound to hemoglobin and myoglobin of diving mammals than in terrestrial humans (15, 63), such that ~9.5 times more hemoglobin is found in diving mammals than in terrestrial mammals (252). Phocid seals store ~65% of intrinsic oxygen in blood, 28% in muscle myoglobin, and 7% in the lungs (119, 166). Despite the numerous interpretational caveats for determining hematocrit and hemoglobin of mammals during diving (see Ref. 30), both increase during diving in numerous species, including those aquatic (36, 102, 246) and human (5, 66, 103, 212). The increase of hematocrit and hemoglobin during diving (202) is largely from reflex-induced contraction of the spleen, which is quite large and capable of storing inordinate amounts of red blood cells in diving mammals (28, 30, 33, 202, 246). Both hematocrit and hemoglobin

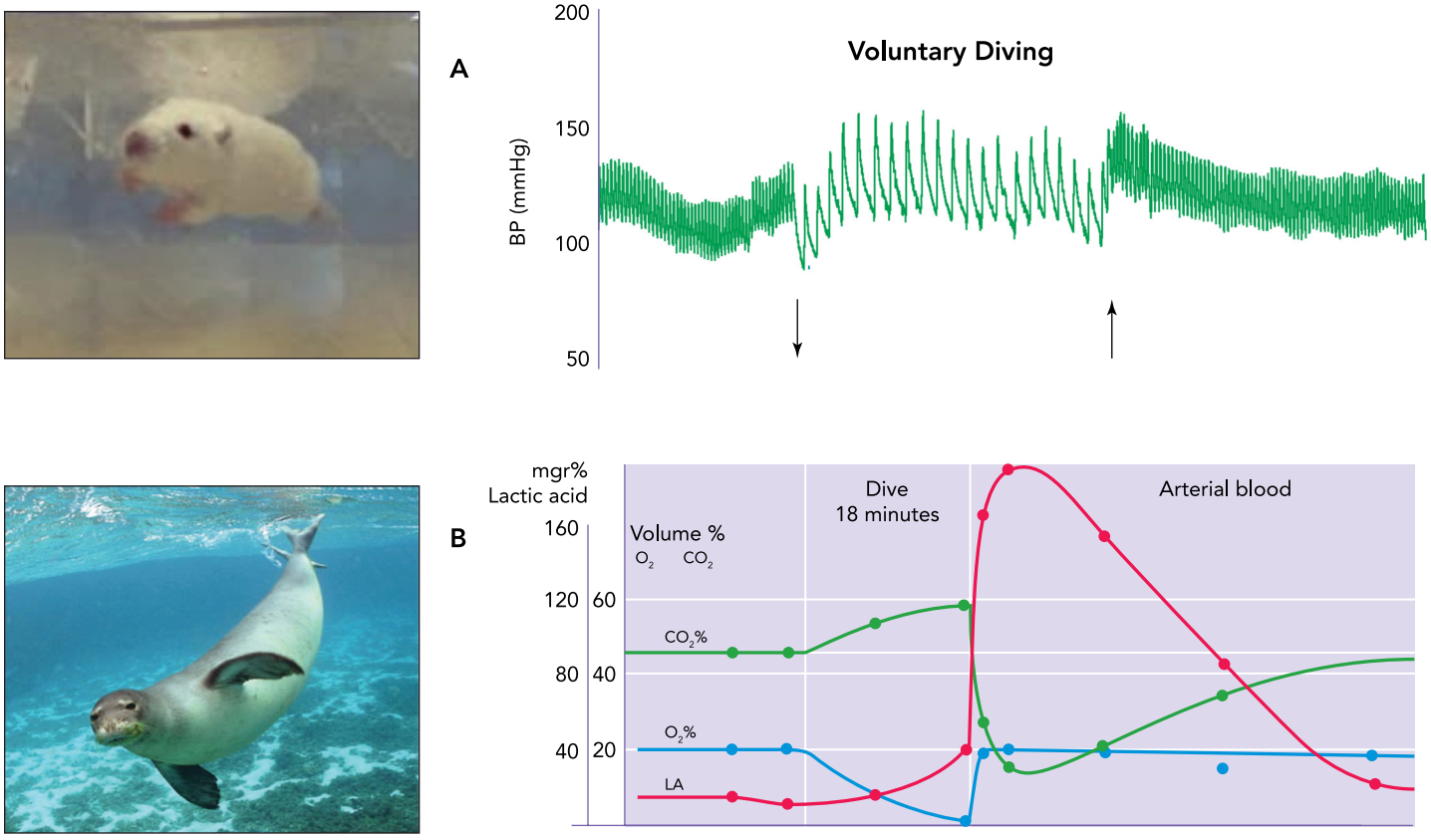

FIGURE 1. **Homeostatic control of cardiovascular hemodynamics and respiration are disrupted during underwater submersion** *A*: note the ~80% drop in HR when a laboratory rat (*top left* photograph) volunteers to dive underwater (down arrow), which persists until it surfaces (up arrow). The transitory increase in arterial blood pressure due to sympathetic activation can also be seen. *B*: respirations also cease during diving, inducing radical changes in blood chemistry. P_{O_2} falls while underwater, whereas P_{CO_2} rises dramatically. Despite this, respiratory chemoreceptors that normally would increase ventilation are muted. The hypoxia in tissues deprived of blood after the selective peripheral vasoconstriction induces anerobic metabolism, with an increase in lactic acid as by-product. Note, however, that its release into the bloodstream does not occur until after the animal surfaces, when the stringent vasoconstriction of muscular, splanchnic, and cutaneous circulations is released. *B* is adapted from Ref. 215 (and is used with permission) showing such changes in a seal (*bottom left* photomicrograph) during a dive.

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also increase in response to seasons and training in semi-aquatic muskrats (137, 138, 139), suggesting increased blood oxygen stores. Besides the increase in hemoglobin and myoglobin in diving mammals, their brains contain other globins (neuroglobin and cytoglobin) that are elevated compared with terrestrial mammals (214, 252). This prompted Williams et al. (252) to propose that marine mammals recruit globins to fight hypoxia by increasing globins in their brains. Since aquatic mammals seldom dive beyond their ADL, however, diving species must utilize their oxygen stores efficiently (35), with globin and hematocrit concentrations varying depending on behavior.

Investigations have shown the larger the myoglobin oxygen store, the greater the aerobic dive duration (119, 172). Muscle biomass is large in aquatic mammals, and its metabolism is dependent on oxygen. Myoglobin is an oxygen-binding protein found in muscle tissue and is especially abundant in diving mammals, reaching 10–30 times that of terrestrial animals (38, 92, 116, 119, 215, 225). Moreover, myoglobin stores of oxygen are especially prominent in active diving muscles of aquatic mammals (115, 116). Myoglobin was found to increase significantly in cultured muscle cells from a Weddell seal in hypoxia (52) vs. control cells, suggesting skeletal muscle cells of the seal have a unique response to hypoxia than a terrestrial mammalian

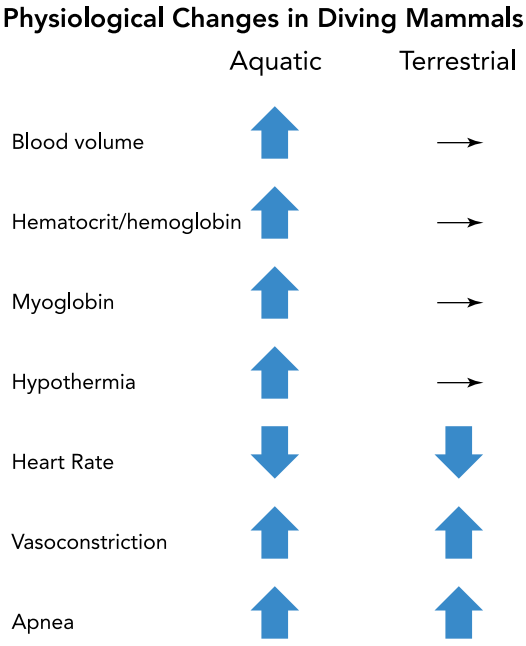

FIGURE 2. **Aquatic mammals develop several changes to augment their intrinsic oxygen stores** The changes aquatic mammals develop to increase oxygen stores and decrease its utilization include increased blood volume, enhanced hematocrit, hemoglobin, and myoglobin, as well as hypothermia. Although such adaptations seldom are seen in land-bound mammals, both aquatic and terrestrial mammals share the bradycardia, vasoconstriction, and apnea characterizing the diving response.

cell line. DeMiranda et al. (52) speculated that a combination of hypoxia, activity, and lipids act in concert to increase myoglobin stores. If diving mammals have resting oxygen saturation levels close to 100 Torr, hemoglobin has a P_{50} (Po_2 at 50% saturation) of ~27 Torr, whereas myoglobin has a P_{50} of 3 Torr (49). Thus myoglobin-bound oxygen during aerobic metabolism will be used only if the muscle becomes very hypoxic; peripheral vasoconstriction makes muscles ischemic and the resulting hypoxia promotes the myoglobin-bound oxygen to be utilized first. The DR thus maximizes the ADL at low levels of exertion. It is unknown whether myoglobin increases in laboratory rats after dive training, however. Thus "globins" increase in hypoxia, whether it be in an athlete training at high altitude or in diving mammals at sea. Utilization of intrinsic oxygen stores recently has been reviewed elegantly by Ponganis et al. (201).

Hypometabolism and Hypothermia

Hypometabolism has been suggested in diving mammals, despite the difficulty in measuring it during undersea excursions (87, 236). Diving mammals experience extreme hypoxic conditions, such that adequate levels of oxygen to supply tissues, especially the brain (205, 214, 252), are compromised. In this regard, hypothermia has been suggested as a metabolic adaptation to decreased oxygen availability (23, 24). Indeed, temperature drops in the brain during diving in seals (16, 174, 217), as does aortic blood temperature (16, 94), slowing metabolism while promoting survival. The depressed metabolism in diving also induces increases in antioxidant defenses to counteract generation of detrimental reactive oxygen species (74, 75).

Although all mammals possess a DR, not all mammals have all these physical and physiological adaptations.

Ontogeny of the Diving Response

Aquatic mammals must quickly develop both behavioral and physiological adaptations to cope with their environment. Seal pups generally explore their aquatic environment first with short shallow dives, but develop longer, deeper dives over time, which aid their foraging skills as adults (4, 17, 21, 114, 137, 157). Behavioral ontogenetic studies in fur seals indicate that diving capabilities are dependent on age for the first 6 mo of life and then generally on body mass (9, 100, 218). As aquatic mammals mature behaviorally and physically, they also mature physiologically to adapt to their environments.

Blood pH is maintained within a tight range by buffers, which neutralize effects of small amounts of acid or base. Diving mammals, however, can

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experience large increases in lactic acid while submerged, especially if they reach their ADL. The buffering capacity of blood of neonatal seals is comparable to that of adults, suggesting that hypoxic intrauterine environments stimulate buffering capacity prenatally (129). Immature cetaceans, pinnepeds, and penguins have only 9–31% of adult myoglobin stores (2, 173), and thus lack concentrations required for extended underwater submersion. However, myoglobin increases with age to adult stores in all species, being completed especially after extended foraging behavior underwater (173). It is thought that physical activity, thermal demands (shivering), and hypoxia all contribute to increased myoglobin. Total oxygen stores also increase seasonally in the semi-aquatic feral muskrat (137, 138), whose increased dependence on underwater diving and hypoxic winter lodges promotes myoglobin formation. However, most of these gains were in blood oxygen capacity vs. insignificant increases in myoglobin (139).

Physiological Responses to Diving

All mammals have nervous systems that regulate homeostatic control over breathing, heart rate (HR), and arterial blood pressure (ABP), but these controls are altered dramatically during diving. Mammals become apneic upon submergence and show an abrupt bradycardia with peripheral vasoconstriction that is maintained during submersion (94). Studying the physiological adaptations of pinnipeds and cetaceans are restricted, however, by limitations of working in pelagic domains on very large animals of many different species with different ontogeny in different environments. Despite these impediments, our interest has been the neural organization regulating these autonomic functions during diving. The question has been raised (49), however, as to why the physiological perturbations to cardiovascular behavior exist at all, considering that most aquatic mammals dive within their aerobic dive limit. Nevertheless, change in HR is both dramatic and temporally linked to diving behavior. Those interested in studying the physiological responses of diving may be better served by studying diving behavior in a rodent such as the common laboratory rat, a small mammal with a reliable diving response (159, 185) and about which much physiology is known. Such studies circumvent the technical impediments imposed on studies of large, pelagic diving mammals (34).

Neural Control of Diving Physiology

Data suggests that the DR consists of three independent neural reflexes regulating respiration, HR, and ABP, respectively. Pharmacological studies using antagonists/agonists show that HR and ABP responses can be blocked selectively while preserving the other two reflexes (62, 168, 254), suggesting the independence of these reflexes after peripheral blockade but implying nothing about their central integration. The three reflexes comprising the DR act harmoniously toward preserving vital oxygen stores and are initiated by activating peripheral receptors. Early studies (54, 60, 79, 106, 108, 125, 130, 213, 244, 249) noted that submersion or wetting of nasal areas was important to induce the DR, and this has been confirmed by others numerous times.

Peripheral Receptive Fields

The autonomic reflexes of the mammalian DR can be induced with only snout immersion, suggesting that primary afferent fibers innervating paranasal areas may be important. Paranasal areas (FIGURE 3), including the anterior nasal mucosa, are innervated by branches of the infraorbital nerve as well as the anterior ethmoidal nerve (AEN) from maxillary and ophthalmic divisions of the trigeminal, respectively (250). Innervation of the nasal mucosa is via free nerve endings from small-diameter fibers (39), many of which contain peptides, notably calcitonin gene-related peptide and substance P (76, 150, 151, 197, 228, 230, 237, 238), derived from trigeminal ganglion neurons (104, 151, 211, 230). Most of these fibers are sensory in function, and many respond as chemoreceptors to local chemical changes induced by inhalation of noxious gases or inflammatory processes (43, 44, 45, 89, 101).

The AEN is considered the "gatekeeper" nerve by us since it is the first to sense noxious gases or water entering the nasal passages. Indeed, transection of the AEN eliminates the bradycardia and attenuates the apnea and ABP changes to nasal stimulation (210). This nerve contains both mechanoreceptors and chemoreceptors (136, 165, 221, 222, 223, 224, 229, 248) responsive to a variety of stimuli, with fibers of small diameter in the Aγ or C range (7, 161) that reach between the epithelial cells toward tight junctions (76, 237). The central fibers of the AEN descend in the ventral third of the spinal trigeminal tract (178, 184) and send fibers into the trigeminal sensory complex. The infraorbital nerve also sends central fibers to all trigeminal sensory nuclei (190), but its distribution is much wider than the AEN. Although currently unknown, it is probable that similar distributions exist in aquatic mammals.

Central Integration

The sensory stimulus is linked to motor output via a reflex arc, "a route followed by nerve impulses in

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the production of a reflex act, from the peripheral receptor organ through the afferent nerve to the central nervous system synapse and then through the efferent nerve to the effector organ." However, peripheral physiologists, who know the stimulus (underwater submersion) as well as the output (apnea, bradycardia, peripheral vasoconstriction) seldom explore central integration.

The trigeminal sensory complex is the principal relay for somatosensory afferent fibers innervating structures in the head (6, 140, 141, 149, 182, 227). The central projections of the AEN have been studied in several nonaquatic species (3, 98, 135, 178, 184, 220). These studies (3, 135, 178, 184, 210) generally show dense projections into superficial laminae of the medullary dorsal horn (MDH) of the

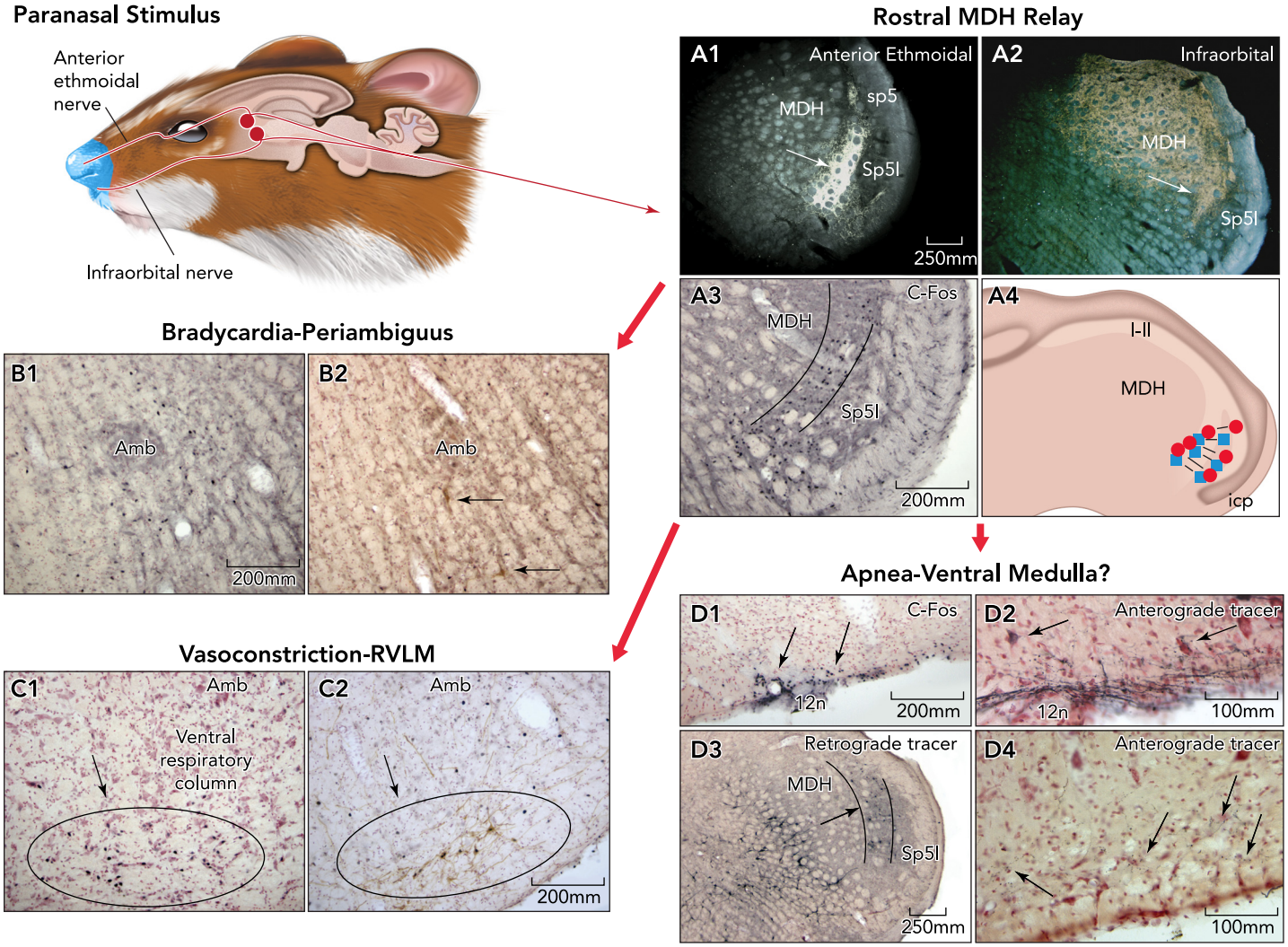

FIGURE 3. **Work on diving rodents suggest paranasal areas (shaded blue) innervated by the anterior ethmoidal and infraorbital nerves are important for initiating the diving response**

These nerves project [A1 and A2 show transport of an HRP cocktail (colored gold) transported transganglionically from the anterior ethmoidal and infraorbital nerves, respectively] into the rostral medullary dorsal horn (MDH) overlapping the caudal subnucleus interpolaris (Sp5I). Note the band of neuropil just dorsal to the Sp5I (arrows) is labeled from either nerve. Neurons activated with cFos (A3; small black nuclei) induced by diving are found in similar neuropil. Moreover, small, bilateral injections of lidocaine (blue squares) or kynurenate (red circles) made into similar locations (A4) blocked the cardiorespiratory responses of nasal stimulation. The hallmark of the diving response is the dramatic bradycardia (see FIGURE 1A); many neurons surrounding the rostral nucleus ambiguus are labeled with cFos after diving (B1), and some of these are preganglionic cardiac motoneurons (B2; arrows point to double-labeled neurons containing cFos and a retrograde tracer injected into the pericardial sac). There also is a massive but selective peripheral vasoconstriction during diving in rats mediated by neurons in the rostral ventrolateral medulla (C1 shows cFos-labeled neurons in the RVLM induced by diving); many such neurons are monoaminergic (C2 showing double labeled neurons with antibodies against cFos and tyrosine hydroxylase). The third neuronal reflex induced by underwater submergence is a profound apnea, which is maintained despite gross disruption of blood chemistry, suggesting inhibition of the respiratory chemoreceptor reflex. Few neurons were activated in the medullary ventral respiratory column (see C1, C2), but projections from the MDH to the ventral surface of the caudal medulla at the spinomedullary junction (D2; approximately −14.6 mm from bregma) overlap where neurons/glia activated by diving are found (D1, arrows; small black profiles show cFos activation). Arrows in D2 point to presumptive neurons with juxtaposed BDA fibers. Injection of a retrograde tracer, which included the retrotrapezoid nucleus labeled small neurons in neuropil similar to that labeled by paranasal primary afferent fibers (D3, arrow). Anterograde transport of tracers injected into these areas of the MDH resulted in extremely small labeled fibers with swellings (D4, arrows) in the retrotrapzoid nucleus ventral to the facial motor nucleus. Similar neurons/glia have long been suspected to be chemoreceptors sensitive to high P_{CO_2}, but details of how they interact with central respiratory neurons is lacking. Other studies (188) have shown the neuronal circuitry driving the diving response is contained within the medulla and spinal cord.

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spinal trigeminal nucleus (FIGURE 3A1), with less dense projections to rostral parts of the trigeminal sensory complex (178, 184). The central projections of the infraorbital nerve (FIGURE 3A2) partially overlap those of the AEN in the rostral MDH (190). Panneton et al. (191) further showed transganglionic transport of herpes simplex virus (HSV-1, strain 29) from the AEN to similar trigeminal areas, as well as transneuronal projections to brain stem autonomic nuclei in the muskrat.

The MDH is an important relay in autonomic reflexes such as the DR (179, 193, 254) and trigeminal depressor response (126, 127, 245, 255). Indeed, underwater submersion activates numerous neurons immunolabeled with cFos in the MDH (158, 183, 186) in locations similar to the termination of primary afferent fibers contained within the AEN and infraorbital nerve (FIGURE 3A3). Moreover, Panneton et al. (179, 193) showed that small injections into similar MDH areas of either lidocaine or kynurenate selectively inhibited the cardiorespiratory sequelae of nasal stimulation (FIGURE 3A4). These data promote this area of the rostral MDH as an important nexus in the reflex circuit driving the DR.

Respiration

Mammals become apneic during diving such that oxygen saturation in the blood drops routinely from 95 to 20% (128, 166, 183, 199, 202) while the animals become increasingly hypercapnic (FIGURE 1). Both changes robustly increase ventilation in animals on land, yet diving animals do not breathe. Diving mammals remain apneic despite gross alterations in blood chemistry (FIGURE 1B) that can exceed their ADL (183), suggesting the homeostatic respiratory chemoreceptor reflex is overridden. Indeed, rats submerged underwater had their Pa_{CO_2} reach 79.2 Torr (normal ~32 Torr) and Pa_{O_2} reach 15.7 Torr (normal ~95 Torr), yet the rats did not breathe (183). Numerous laboratories are exploring for neurons mediating the respiratory chemoreceptor circuit, but this circuit has not been characterized to date. The neuronal circuitry driving respiration is complexly organized, and its efficiency in fulfilling physiological needs is incompletely understood (72), but a reflex apnea induced with nasal stimulation persists despite truncating the brain at the pontomedullary junction (188), suggesting the neurons are contained within the medulla and spinal cord. Although influences over reflex behavior are manifested by many suprabulbar neurons, including those important in apneic reflexes (41, 55, 56, 57, 58, 203, 204, 247), we consider them modulators rather than intrinsic to the reflex diving circuit.

Indeed, respiratory behavior persists in many slice preparations of only the medulla (11, 72, 206). The medullary ventral respiratory column (8, 71) holds many respiratory neurons, and one part of it, the PreBötzinger complex, is where many neurons generating rhythm lie (11, 72, 206). Neuroanatomical projections from the part of the MDH that receives paranasal afferent fibers (184) were relatively dense to caudal parts of the ventral respiratory column where expiratory neurons dominate. More sparse projections from the MDH also were seen in the pre-Bötzinger complex (184), the retrotrapezoid nucleus (FIGURE 3D3 AND D4), and the ventral surface of the caudal medulla near the spinomedullary junction (FIGURE 3D2); the latter two groups overlapped with cells labeled with Fos in diving rats (FIGURE 3D1; Ref.183). Although there were but few neurons labeled with cFos in the ventral respiratory column (FIGURE 3C1) after underwater submersion (183), more anterograde labeling was juxtaposed to cFos-labeled "epi-glia" cells (183), and in the retrotrapezoid nucleus (FIGURE 3D4), where potential general and respiratory chemoreceptors were found throughout the medulla's ventral surface and activated by underwater submersion. Such putative chemoreceptors are linked by gap junctions (51, 235) and may provide a fast link to the brain stem respiratory network. Idiosyncrasies of the cFos technique must be considered, however (see Ref. 186 for discussion).

The inhibition of respiration while submerged despite gross fluctuations in blood gases is powerful. A persistent apnea also is created when somatostatin neurons in the pre-Bötzinger complex are silenced (241), and these same somatostatin-expressing neurons project throughout the ventral respiratory column as well as at other sites including the retrotrapezoid nucleus (242). Although the projection from the MDH to the pre-Bötzinger complex is relatively sparse, it is possible that it plays a role in inhibiting the respiratory network by both inducing and maintaining an apnea, but this must still be proven.

Heart Rate

The dramatic bradycardia seen with underwater submersion (FIGURE 1A) is mediated via the parasympathetic vagus nerve. Most parasympathetic preganglionic cardiac motoneurons are found in the external formation of the nucleus ambiguus (99, 192, 243) that provide B-fibers to principal neurons in cardiac ganglia (42, 156, 207). Double-labeling cardiac motoneurons (181) with cFos after voluntary diving and cholera toxin after retrograde transport showed most of them surrounding the rostral nucleus ambiguus (FIGURE 3B). Although cardiac motoneurons maintain several peptide and glutamate receptors (12, 13, 46, 110, 148), work in

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in vitro slices show preganglionic cardiac motoneurons activated by stimulation of the trigeminal tract are modulated by serotonin (84) and acetylcholine (85) receptors. However, our functional anatomical studies provide little information concerning from where cardiac motoneurons receive their input. Although our earlier studies (179, 193) suggest a relay from superficial neurons in the rostral MDH as important for mediating HR, ABP, and respiration to underwater submersion (see FIGURE 3A), the function of primary afferent terminals of the anterior ethmoidal nerve, which project beyond the trigeminal sensory complex (178, 184) into the reticular formation near the rostral nucleus ambiguus and rostral ventrolateral medulla, is still unknown.

Although the function of these fibers must still be explored, apparently many contain calcitonin gene receptor peptide and TRPV1 (40); some may provide direct projections to cardiac motoneurons. Moreover, investigations on postganglionic cardiac motoneurons driven by nasotrigeminal stimulation have commenced (155). McAllen et al. (155) recorded from principal cells in the cardiac ganglia of a working heart-brain stem preparation and showed their activation after applying cold Ringer's solution to the snout. They also concluded that convergence occurs before the postganglionic principal cells from various reflexes influencing cardiac function (arterial baroreceptor, peripheral chemoreceptor, and diving), probably within the brain stem.

Regional Blood Flow

The redistribution of blood supply in mammals in response to diving shunts blood away from hypoxia tolerant tissues to those with greater oxygen need, including in diving rats (175, 176). Blood supply to tissues/organs of diving animals is exercised at the level of arteries rather than precapillary arterioles (29), reducing the effect of vasodilator metabolites released by ischemic tissues. Indeed, near-zero conductance through the abdominal aorta has been shown in seals during diving (18). The delayed release of lactic acid during recovery (FIGURE 1B) is attributed to a striking redistribution of blood away from muscle during submersion and reperfusion after emersion. It is well known that the sympathetic nervous system controls such distribution of blood.

Numerous studies have shown that neurons in the rostral ventrolateral medulla (RVLM) regulate ABP by maintaining sympathetic tone. Moreover, studies have implicated the RVLM as the brain stem relay to the spinal cord for the baroreceptor reflex (88, 164, 219) and somatosympathetic reflexes (20). The early increase in ABP with underwater submersion activates the baroreflex but does not include baroreceptive circuitry until the RVLM since bilateral injections of kynurenate made either into the dorsolateral solitary nucleus or the caudal ventrolateral medulla (164) greatly attenuate the baroreflex but fail to modify responses from nasal stimulation. However, similar injections into the RVLM greatly reduce effects of nasal stimulation on sympathetic nerve discharge but not effects from baroreflex activation (164), since baroreceptor circuits at this level utilize GABA as a transmitter. The RVLM contains the C1 adrenergic cell group (209), and many of these neurons (FIGURE 3C2) are activated by underwater submersion (163). However, both adrenergic and nonadrenergic spinally projecting neurons in the RVLM are responsive to nasal stimulation (164). Moreover, ~62% of the same baroreceptive RVLM neurons normally silenced by increases in ABP are excited by nasal stimulation despite increases in ABP, suggesting that the homeostatic baroreceptor reflex is overridden. The fact that the vasoconstriction imposed by underwater submersion is not universal to all tissues suggests that a general sympathetic activation does not occur. Moreover, regional specificities to different vascular beds have been proposed in the RVLM (48, 153, 154). Smaller diving mammals such as rats are compatible with laboratory experiments (159, 185) and can be utilized to explore this phenomenon better.

Suprabulbar Control of the Diving Response

Aquatic mammals have repeatedly shown that they "control" the bradycardia induced, despite the fact the heart is a visceral organ generally considered under autonomic, or automatic, control. Indeed, we initially decided to study the mammalian DR after seeing that seals showed an abrupt bradycardia before underwater submersion and a tachycardia prior to emersion (32). Such control over their "autonomic" nervous system has been noticed by diving physiologists for some time (15, 16). Indeed, seals often either show little bradycardia when diving voluntarily, reduce heart rate in anticipation of underwater submersion (32), induce a bradycardia to auditory, photic, or painful stimulation (108), or show an anticipatory tachycardia before emerging (15, 32). Moreover, sea lions conditioned to adjust their autonomic nervous systems to auditory or visual commands suggest they may "will" bradycardia (200, 208), probably from suprabulbar sites. Control of bradycardia develops through ontogeny (37, 68, 86, 90, 100, 107, 157, 170), and minimum HR is increased in older animals compared with younger cohorts (86, 170) but has a caveat in that dive duration is generally longer in mature animals that have more mature adaptations in

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blood volume, myoglobin, etc. Bradycardia of diving is also variable in dolphins depending on behavior. If a submerged mammal is exercising, the degree of bradycardia developed is dependent on exercise levels (50, 171); the diving bradycardia is modulated by behavior and exercise in a predictable manner (171).

Since underwater submergence is the usual stimulus inducing the DR in awake animals, many investigators performed "forced" submersions, where the animals were tethered on boards or placed in cages and dunked underwater (54, 59, 94, 111, 113, 120, 125, 130, 131, 147, 185, 213, 216). Many of these studies noted the hemodynamic responses were subtly dissimilar to voluntary submersions (94, 111, 162, 244). HR generally reaches a nadir quickly in forced submersions and remains depressed until the animal surfaces. However, the bradycardia of aquatic mammals diving voluntarily and with but moderate exercise is more variable and less intense than that seen in forced diving (54, 111, 119, 162, 185), but the bradycardia of involuntarily dunked rats is not different than voluntarily diving rats (185). Although such differences suggest neural control beyond the level of reflex and implicate suprabulbar control in large aquatic mammals, it suggests the response in the rodent is more reflexive in nature.

It is possible that preventing an organism from deciding its own fate by involuntary submersion may induce either fear or stress in several species (31, 78, 231, 233, 234, 257), and these emotions may alter normal reflex responses. McCulloch and colleagues (160) concluded that forced submergence is stressful to both naive and trained rats, but voluntary diving in trained rats is no more stressful than being handled by humans. The bradycardia seen in rats is locked tightly to the time submerged, but hemodynamic changes were more variable in dunked naive rats and included more arrhythmias (183). It is of interest that co-activation of both parasympathetic and sympathetic cardiac nerves induces cardiac arrhythmias (194, 195, 226). Although the bradycardia of voluntary diving is vagally mediated and dominant, forced underwater submersion stresses the animal and probably also activates the sympathetic nervous system from sources beyond reflex diving. Perhaps the numerous arrhythmias seen during forced diving are induced by suprabulbar sources and counter the bradycardia of underwater submersion.

It is of interest that cetaceans and pinnepeds have brains that approach human brains in complexity with highly convoluted cortices (65, 96, 97, 142, 143, 144, 145). Although the DR apparently has minimal suprabulbar modulation in rodents, we suggest suprabulbar neurons in higher species may indeed direct autonomic behavior seen in the DR. The importance of such control highlights deflection from dogma that control of the "autonomic" nervous system is involuntary. Harnessing the suprabulbar circuits of origin that control diving physiology may promote feedback therapies designed to remedy high HR and hypertension associated with anxiety.

Summary and Perspectives

The autonomic changes resulting from underwater submersion are dramatic and swift, suggesting reflex circuitry with little integration and few synapses in rodents. If the area of the rostral MDH where primary afferent fibers innervating paranasal areas project is considered the locus from which the cardiac, blood pressure, and respiratory consequences of underwater immersion emanate, the route of such fibers toward the brain stem targets mediating the responses must be considered. First, the very small neurons found in the aforementioned MDH neuropil are considered the rostral extension of the substantia gelatinosa (laminae I and II), which has been misplaced dorsally and medially by the caudal pole of the subnucleus interpolaris. Lamina II neurons are very small, and very few have been shown to be projection neurons. However, many with paranasal receptive fields indeed are projection neurons going to cardiorespiratory brain stem nuclei, implicating the importance of the DR and supporting a role in early mammalian evolution. We show numerous projections from these neurons (see Ref. 184 and FIGURE 3D3) to areas of the medulla regulating cardiorespiratory behavior. These small neurons also probably have very small axons see (FIGURE 3D4); if they are below 1 μm in diameter, they are beyond the resolution of the light microscope, which implies their identify must be obtained by other means.

That said, the increase in arterial blood pressure with diving probably is mediated by very small fibers projecting from neurons in the rostral MDH to the RVLM. The caudal pressor area (239, 240) also receives such projections (187) but apparently does not mediate the increase in arterial blood pressure since pressure increases are still seen with nasal stimulation after inhibiting injections of glycine, muscimol, or ibotenic acid (189) are placed in this caudal pressor area. Although retrograde transport of tracers injected into the RVLM is found in numerous neurons in this paranasal part of the MDH, such projections were not matched in intensity by the relatively sparse anterorgrade transport from the MDH (184). This perhaps also may be due to the extremely small axons of these MDH neurons, making them difficult to see with the light microscope. The ventral respiratory column and other

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associated respiratory-related nuclei (e.g., ventrolateral solitary nucleus, retrotrapezoid nucleus) were all labeled using retrograde and anterograde transport techniques, albeit sparsely with anterograde methods and mostly by small-diameter fibers. Although there were but few neurons labeled with cFos in the ventral respiratory column, numerous neurons considered presumptive chemoreceptors were labeled. We suggest that apnea of diving is induced by inhibitory MDH projections to the pre-Bötzinger complex, but this still must be proven. The bradycardia of diving must at least partially be relayed through the MDH, since it can be inhibited after injections there but with the caveat that injections of ibotenic acid into the nearby caudal pressor area also eliminate the bradycardia to nasal stimulation. The role played by the extratrigeminal projections of the AEN into the rostral and caudal ventrolateral medulla must still be deciphered, but these also may augment the cardiovascular responses.

The DR in humans often is deployed in biology/physiology laboratories since HR is easily monitored (19, 93). The HR responses of such exercises, however, are variable, perhaps because of suprabulbar control over this reflex behavior (253). Nevertheless, the DR is prominent in human neonates (82, 196) and is suggested as the etiology of "cold water drownings" (80, 83, 91), the Sudden Infant Death Syndrome (1, 133, 134, 152, 232), as well as important in apnea attacks in children (61, 81, 117). The DR is the most powerful autonomic reflex known, and further study of this phenomenon, especially its neural control (180), may be fruitful for understanding how the brain controls autonomic behavior. It is also important to explain why the DR is universal in all vertebrates. Is the purpose of this enigmatic response designed to preserve life by conserving oxygen? Is it the "master switch of life" (216)? Although neurophilosophers can debate these issues, physiologists perhaps could explore genetic databases to determine whether code was developed very early in the evolution of vertebrates to promote species survival. The remarkable mammalian diving response is a chapter worth studying. ■

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