The multibranched nerve: vagal function beyond heart rate variability

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ABSTRACT

This paper reviews the many functions of the vagus nerve, to understand how they interact in daily life and what might be accomplished by therapeutic electrical stimulation. A short historical introduction on the discovery and name-giving of the cranial nerves numbers 9-12 is followed by an overview of the functions that are under lower brain stem control: heart (rate, contractility), intestine (swallowing, peristalsis and glands secretions, feeling of satiety), lungs (bronchoconstriction, lung-irritant and stretch receptor signaling), blood pressure (by vascular wall stress sensing) and blood gases by specialized receptors. Key in the review is the physiology behind beat-by-beat heart rate variations, how everyday life is reflected in its variability, from exciting moments to quiet sleep, with the ‘common faint’ or vasovagal collapse as extreme example. Next, the recently proposed role of the vagus nerve in limiting inflammation is discussed. This has led to adoption of an earlier developed technique for epilepsy treatment, i.e., electrical stimulation of one vagus nerve bundle in the neck, but now for immune diseases like rheumatoid arthritis and the scope is even widening to depression and cluster headache. However, the problem in application of whole vagus nerve stimulation is the lack of specificity: there is no way to titrate the stimulation to an observable effect variable. All nerves in the bundle, incoming and outgoing, can be ‘hit’ leading to side-effects which limit the intended application.

Alternatively, relaxation-oriented therapies recently stress the importance of ‘getting into a vagal state’ to invoke often much the same effects, but now in a more physiological way.

This paper is a sequel to earlier reviews on autonomic nervous function and interpretation of heart rate variability (Karemaker, 2017, 2020). The present one gives an overview of the many functions supported by vagal branches, and the possible effects of their activation, be it as sensory afferents (carrying incoming signals - the majority of the fibers - (Neuber & Berthoud, 2021)) or motor efferents (for outgoing commands). A short historical introduction seems in order to understand the many difficulties posed to anatomy and physiology of this nerve to get a grasp of its many functions.

2. Note on the origin of the name “Vagus Nerve”

The vagus nerve probably got its name around 1600: the first one known to have written it down is Caspar Bartholin the elder (1585–1629). In his Anatomicae Institutiones Corporis Humani from 1611, Bartholin calls the nerves that leave the brain as the tenth pair, “to others the sixth pair, or vagus” (“Nonum par, aliis sextum & vagum”, p.405). Implying that the name was already in use by others, but he does not tell by whom. At any rate it had not been named as such by the father
of modern Anatomy, Andreas Vesalius (1543). Fig. 1 is taken from Vesalius’ work De Humani Corporis Fabrica, showing the extent of branching, stretching from the brain to deep in the abdomen. Probably the analogy with the rambling variety of plants called “vagus” in Latin was so obvious to these scholars who were trained in medicine and medicinal botany, that this prompted the nerve’s nickname. At the time of Bartholin, the matter of which nerves to view as separate cranial nerves had not been settled. He himself added the olfactory nerves as the first pair to the ones that were recognized as cerebral or cranial nerves in his time, counting the vagal complex as ninth, now the tenth cranial nerve.

3. Early development of the vagal complex and some comparative physiology

A short overview of early embryonic development may help to clarify the formation of the complex nerve construct that transpires through Vesalius’ picture (Fig. 1). Fig. 2 depicts the situation when the embryo is some 5 weeks old. The embryo looks bent around its primordial heart and liver. In the head/neck transition, a series of tissue folds can be observed that would turn into branchial arches if it were a fish. However, in mammals the tissue masses of the folds and the primary gut dorsal to these give rise to a wide variety of organs, which will be found later at various places from this position downward. These organs will remain innervated by the nerves that supply this part of the embryo, irrespective how far away from their origin they end up. That explains why the nerves sprouting from the medulla oblongata (glossopharyngeus nr.IX; vagus nr.X; accessorius nr.XI; hypoglossus nr.XII) have this widespread scope of action. It also explains the left-right division between branches of the same pair of cranial nerves. The vagus nerve has by far the largest scope, in view of its intimate connection with the heart and the derivatives of the primordial gut.

The derivatives of these structures in the region of the transition from head to trunk are manifold, (Table 1). The table demonstrates the extensive area of innervation and width of functions served by this part of the medulla oblongata and, in particular, by branches of the vagus nerve. The table is, however, incomplete: the vagus is also considered to have a function in immune defense. This issue will be elaborated upon below.

4. Heart rate and vagal activity

In the column ‘Visceral functions’ of the vagus nerve ‘deceleration’ (of heart rate) is mentioned as the result of parasympathetic activity to the heart. More nerve activity, lower heart rate. As a branchial or gill-reflex, vagal activation is of utmost importance to fishes: if their one-chambered heart generates too high a pressure, the fine capillary networks in the gills, where exchange of oxygen and carbon dioxide with the surrounding water takes place, would be put at risk. Starting at the heart, the gills are the first organ to be perfused, thereafter the oxygenated blood comes together in the dorsal aorta, applying the residual pressure for the perfusion of the rest of the body. Pressure fine-tuning is, therefore, essential: too high and the gills are in danger, too low and the other organs suffer. In particular, the protection of the gills requires immediate action: within one or two beats cardiac slowing must drive the high pressure down; this is what the cardiac vagus accomplishes. Conversely, low pressure will lead to vagal withdrawal. Sympathetic activation at low blood pressure in fishes is only marginally developed, and comes into action for instance at low oxygen levels of the water (Taylor, Jordan, & Coote, 1999).

In animals with lungs and a two-chambered heart, this branchial reflex is still maintained, known as the baroreceptor reflex or baroreflex. The afferents are from stretch receptors in the carotid sinuses (remnants of the fourth branchial arteries), fibers traveling in the glossopharyngeal nerves and in the aorta and pulmonary trunk (sixth branchial arteries), fibers in the vagus nerves. Although the prevailing pressure levels have

Fig. 1. : Plate 49 from Andreas Vesalius’ “De humani corporis fabrica” (1543). The previous plate in this work showed the brain from its lower surface. In the description to this one, Vesalius explains that it shows the whole brain and the cerebellum, with the first cranial nerves from the right side, as well as the last cranial nerves both from the left and right side, in view of their left/right differences. For the latter ones he depicts them as viewed in the body from the front, as if the face looks to the left arm, showing thorax and abdomen; the urinary bladder would be the lowest part. Vesalius includes the sympathetic trunk in this drawing; he observed many connections between the two systems and reasoned that a nerve from the brain could not serve such an elaborate area without support from many levels. Therefore, the picture actually shows a combination of the (cranial) parasympathetic and sympathetic systems.
changed in evolution, the reflex acts still in about the same way via the cardiac vagal control center in the medulla oblongata: a high systolic blood pressure pulse will immediately be counteracted by vagally induced cardiac slowing.

5. Interlude on blood pressure control

A short exposé on blood pressure control is in place, Fig. 3 A explains the basics. Center stage is Ohm’s law, Voltage (V) = Current (i) x Resistance (R), or V = i x R, formulated for blood flow as Mean Arterial Pressure (MAP) = Cardiac Output (CO) x Systemic Vascular Resistance (SVR), or MAP = CO x SVR. Note: the formula does not take the pulsations of blood pressure into account, it only looks at mean pressure. CO, the amount of blood pumped out by one ventricle in one minute, can be equated to Heart Rate (HR) x Stroke Volume (SV), or CO = HR x SV. In the schematic of Fig. 3 A these three factors control blood pressure. There are 2 main loops: 1) one via the nerves (middle, in red), 2) the other one via volume control (below, in light green). The higher centers of the brain have overriding control, (top, marked in blue). Note that activation is symbolized by a pointed arrow, inhibition by a filled circle; for instance, HR will be lowered by vagal activity and increased by sympathetic activity; the sympathetic system mainly works via its effects on vascular smooth muscle. On the arterial side by increasing resistance due to decreased diameters of small arteries and arterioles, thus slowing down blood pressure decrease in the diastolic phase; on the venous side by compressing the volume of blood remaining in the large capacitance veins, thereby increasing the filling of the heart from the veins to increase stroke volume.

Let us follow the flow of information and nerve activity in Fig. 3 A: Starting at the nerves from the baroreceptors at the left, they activate cells in the first station: the nucleus of the solitary tract in the medulla oblongata. From here, via short pathways, cardiac vagal motor neurons in the nucleus ambiguus are activated, more vagal activity at more baroceptor activity (i.e., higher pressures). At the same time, sympathetic centers close by are inhibited. Once this inhibition is lifted, when the baroreceptors are silenced in the diastolic phase, sympathetic activity will be increased. On the arterial side by increasing resistance due to decreased diameters of small arteries and arterioles, thus slowing down blood pressure decrease in the diastolic phase; on the venous side by compressing the volume of blood remaining in the large capacitance veins, thereby increasing the filling of the heart from the veins to increase stroke volume.
outflow becomes possible, sooner within the beat at lower diastolic pressures. These two principles, for cardiac vagal and sympathetic outflow, are clarified in Fig. 3B. Due to its spontaneous depolarization in the resting period, the sinus node, located in the right atrium, is the pacemaker of the heart. The vagal volley comes into effect almost immediately, even delaying the next heartbeat when coming early enough in the cycle of the sinus node (DeBoer et al., 1987; Jalife & Moe, 1979; Karemaker, 2015). The effect of the sympathetic nerves, however, comes only into action after some two beats (Hill-Smith & Purves, 1978), and will last for the next few beats. The effect of sympathetic nerve activity on a specific heart period is, therefore, composed of those from a couple of previous beats, as schematized in Fig. 3C. The effect of excretion of adrenaline into the bloodstream is still slower and takes about a minute to make itself felt. Due to the briskness of vagal activity and the relative slowness of sympathetic activity, the jitter of heart rate from one beat to the next is almost exclusively due to parasympathetic, that is vagal, activity.

Low pressure will silence the cardiac vagus and allow for sympathetic outflow to heart and vessels. It must be noted that the question of how much sympathetic outflow is generated is not set by the baroreflex, but by other mechanisms (Sun & Guyenet, 1986), as symbolized in the ‘blue section’ of Fig. 3A: like psychological activity, or firing of chemoreceptors or metaboreceptors during exercise. If, for instance under anesthesia, central sympathetic drive is low, no or insufficient sympathetic outflow will occur when blood pressure drops; the silencing of baroreflex afferents may allow sympathetic outflow, but it does not, by itself, dictate how much activity (Souza et al., 2021). Therefore, there is an important role for the anesthetist to control blood pressure by vasoactive drugs.

6. Cardiorespiratory coupling and Respiratory Sinus Arrhythmia

In fish, heart and respiration are interacting: heart rate and buccal movement to press fresh water through the gills have about the same frequency and, in the resting situation, are in synchrony, thanks to the vagus (Taylor et al., 1999). In animals with a pulmonary and systemic circulation (like mammals), decreased central vagal command drives heart rate up during inspiratory drive (Farmer et al., 2016). Additionally, the baroreflex will modulate heart rate with the pressure excursions that accompany inspiration and expiration (DeBoer et al., 1987), also manifest in Fig. 3C (notice the variation in shorter and longer heart periods, that are, in fact, in phase with inspiration and expiration). As a consequence, respiratory sinus arrhythmia (RSA; changes in heart rate with respiration) is a common phenomenon throughout all vertebrates (Taylor et al., 1999).

In the resting situation, heart rate is mainly under vagal influence: on average it is much lower than the “intrinsic rate” (e.g. 72 vs 105 bpm), the latter would occur in the absence of any autonomic influence (Jose & Collison, 1970). That implies that increases and decreases of vagal activity are sufficient to decelerate or accelerate heart rate, respectively, no intervention by sympathetic activity required. The most prominent heart rate variations in the resting state are due to respiration; they even continue during a voluntary breath-hold at a slightly lower frequency (Penáz & Buriánek, 1963). However, there are also other,
7. HRV other than due to respiration, what is vagal tone?

What is it that makes heart rate and its variability so special? Why is the science to quantify HRV so elaborate, and why does it penetrate so many aspects of medicine and psychology (Karemaker, 2020)? I can see two main reasons: 1) it is a relatively easily obtainable signal and 2) there is the common notion that lower heart rate goes along with being more ‘at ease’ with the aura of ‘healthier’. This has even led to the term ‘vagal tone’ which should preferably be high in a relaxed person. Vagal tone is probably an analogy to the neurological term ‘muscle tone’ or tension, which depends on the number and frequency of activated fibers in a muscle, influencing its resistance to stretch and deformation, also observable to the touch: relaxed or stiff muscles. It is difficult to imagine how this translates to the amount of vagal activity as it appears in heart rate and its variability. Does a large magnitude of phasic HRV (including RSA) indeed represent high vagal activity throughout the body, or is it sufficient to look at prevailing/average heart rate or maybe a combination of many determinants? That is where much of the confusion and disagreement starts: how to quantify an ill-defined quantity? HRV, furthermore, has obtained the status of a crystal ball, thanks to the multiplicity of techniques for its calculation that, each with its own merit, claim to diagnose many disorders.

Expanding on the introductory paragraphs, one might take a systems analysis approach and start looking for the ensemble of functions that is regulated from the medulla oblongata, as depicted in Table 1. The main function of the pharyngeal/vagal complex is in food intake and digestion, next in respiration and metabolism (lungs, liver, heart). So, a high ‘vagal tone’ in favor of these activities does not necessarily go along with a state of relaxation for the heart. For that reason, test participants are asked to have their (light) meal at least some two hours before an observation, when they are supposed to be ‘at rest’, and strenuous physical exercise or caffeinated drinks in the run-up to the measurement are not allowed either. And even then, one cannot prevent worrying thoughts from popping up, ruining an otherwise perfect ‘resting state’ observation. In that vein it may seem handy to impose a respiratory rhythm by pacing the rate and have the participant just focus on the breathing. However, in our hands that always brings about some degree of hypo- or hyperventilation, despite our best efforts to prevent that from happening (Stok et al., 2019).

8. Central nervous command of vagal outflow and HRV

The main source of efferent cardiac vagal activity in most mammals is the *nucleus ambiguus*, ventrolateral in the medulla oblongata (cf. Fig. 3 A). However, the distribution of cardiac vagal motoneurons between this and the *dorsal motor nucleus of the vagus* is variable between animal species (Neuhuber & Berthoud, 2021). The *dorsal motor nucleus* is mainly concerned with processes like secretion of pancreatic enzymes and promotion of peristalsis and digestion along the gastrointestinal tract as mentioned in Table 1 (Farmer et al., 2016; Hsieh et al., 1998; McAllen & Spyer, 1976; Pates tas & Gartner, 2000).

What makes cardiac vagal outflow so variable? Fig. 3 explains how variations in blood pressure are translated into heart rate variations by way of the baroreceptors that send their bursts of afferent nerve impulses to the nucleus of the tractus solitarius in the medulla oblongata. If all things would remain constant, a constant level of blood pressure and pulse pressure at each beat would lead to a constant interbeat interval, its duration being dictated by the number of incoming baroreceptor impulses only. By contrast, variability in this incoming stream of information from the baroreceptors and how the medulla oblongata (under control of higher centers) translates this information, will show up as variability of interbeat intervals. If there is ongoing nerve traffic along other pathways to the medulla oblongata, like incoming vagus nerve information from colon movements (Yuan et al., 2020), muscle or skin afferents, the reflex response in cardiac vagal outflow may be increased or suppressed (Iriuchijima & Kumada, 1964). This variability from within or in the transfer from input to output is further exaggerated by parameters of the respiratory cycle (e.g., respiratory rate and volume), (Farmer et al., 2016; Grossman, Karemaker, & Wieling, 1991; McAllen & Spyer, 1978; Spyer & Gilbey, 1988).

Is this sufficient explanation for the beat-to-beat variability of heart rate? Not yet mentioned are changes in central nervous conditions, like anxiety, social interaction, etc. These, each in their own way, may cause changes in transfer to cardiac vagal outflow alluded to in the previous paragraphs. Much of this can be short-lasting, hardly noticed by the person, but nonetheless evident in heart rate variations. In extreme cases, emotional states may induce strong dominance of either sympathetic or parasympathetic outflow, leading to a hypertensive crisis or vasovagal syncope respectively (see below).

Finally, the interaction of sympathetic and vagal activity at the autonomic pleaxes innervating the sinus node of the heart is of decisive importance for the ‘briskness’ of heart rate variations: (Edman et al., 1995) showed that co-stimulation of sympathetic efferents to the heart depressed the extent of vagally mediated heart rate excursions at the respiratory frequency. The extent of beat-to-beat excursions also depends on the arrival time of the vagal information at the sinus node: critically timed bursts of impulses may induce unexpectedly large differences from one beat to the next, compared to the effects of bursts coming early or late in the cycle (Karemaker, 2015).

9. Vagal activity during sleep

Sleep demonstrates how heart rate variability depends on the condition of the central nervous system. Sleep can be discriminated in defined stages by the combined measurement of an electroencephalogram, electro-oculogram and an electromyogram, as follows: light sleep (S1), slow wave sleep (S2, S3-deep sleep) and rapid eye movement (REM-) sleep (Kryger, Roth, & Dement, 2017). In Polysomnography for the detection of respiratory disturbances during sleep, appropriate transducers are added to this array. Healthy, undisturbed sleep occurs in cycles where the pattern of S2 to S3 to REM is repeated once per 1–1.5 h. Concurrent with the transitions from S2-S3, vagal effects on heart rate increase, while sympathetic activity decreases (Hornyk et al., 1991). In deep sleep a striking constancy of respiratory rate is observed, almost like a ticking clock (Cabiddu et al., 2012; DeBoer, 1985). Of note, Smyth, Pickering and Sleight found increased baroreflex sensitivity (BRS) during sleep, in line with uninhibited vagal responses to incoming baroreceptor traffic (Smyth, Sleight, & Pickering, 1969). The effects on heart rate and HRV of the various sleep stages are so well discernable that software developers for the increasing number of wearable devices are trying to exploit these to increase the yield of personal information for their users (Hamill et al., 2020; Pagan et al., 2021).

10. (Vaso-)vagal syncope

Overactivity of the cardiac vagal branch may lead to extreme cardiac slowing or even 10–15 s or longer cardiac arrest, accompanied by loss of consciousness and fainting with muscle weakness (van Lieshout, Wieling, & Karemaker, 1997). This condition may or may not be accompanied by sympathetic withdrawal, adding to the loss of pressure in the systemic circulation. Alternatively, sympathetic withdrawal may be the predominant phenomenon. It is still a puzzle to be solved what causes these cases, which have received the nickname of ‘the common faint’. In most of our cases a faint is preceded by increasing heart rate but decreasing blood pressure, due to decreasing return of blood to the ventricles. Since many cases occur during standing, the resulting fall to the ground has one positive effect: blood returns to the heart and the heart does not have to pump against gravity. However, a vasovagal
response may also occur in the supine position, in particular in a test situation designed to mimic orthostasis without the supervening effects of hydrostatics: lower body negative pressure (LBNP). Here, the participant is supine, with his lower body enclosed in a box wherein a subatmospheric pressure is generated, causing blood to pool like in the standing position. Fig. 4 shows an example from such a test from our own database where a near-syncopal event occurred.

Not all faints are due to prolonged orthostasis, they may also be caused purely by psychological factors: blood phobia is a good example. In those cases, the supine position will lower the chances of fainting as well (Mednick & Claar, 2012). A good countermeasure to combat impending syncope due to insufficient venous return is to tense buttocks, leg- and abdominal muscles (Krediet et al., 2002). Unobtrusively, speakers at the rostrum can do this when they cross their legs and tense the same muscles; alternatively, walking around across the stage may help as well. Referring to Fig. 3 A, these countermeasures are mainly acting on venous filling, thereby providing sufficient blood to the heart for diastolic filling.

The background of the vasovagal syncope as a ‘playing dead’ reflex is still unclear (van Lieshout et al., 1997), the idea that it happens when it is better to seem dead than to be dead. On the other hand, in orthostatic hypotension, the combination of decreasing blood pressure with increasing heart rate points to low stroke volumes at a high sympathetic activity to the cardiovascular system may become inhibited (Yuan et al., 2020). These examples exist that show (generally weak) correlations between for instance HRV and other bodily functions or psychiatric conditions. However, that does not prove the issue at hand, i.e. are the various vagal outflow channels in synchrony?

It has been mentioned above that the cardio-inhibitory vagal motor-nerves in most mammals are predominantly found in the nucleus ambiguus and fewer (if any, depending on species) in the dorsal motor nucleus (McAllen & Spyer, 1976). The dorsal motor nucleus is importantly involved in regulation of the intestine. The differences in innervation of cardiac autonomic plexuses by cells from either nucleus and their physiological effects has been the subject of extensive studies in rats by Cheng and colleagues (Cheng et al., 2004). In their research both nuclei project to the heart, but the (thin) fibers from the dorsal motor nucleus have only small heart rate effects, if any. When the nucleus ambiguous is deleted, the vagal response to baroreflex stimulation is gone. From the Cheng and other studies, the image appears that the nucleus ambiguous is the one most involved in the fast and phasic control of heart rate by the vagus nerve. The dorsal motor nucleus cardiac fibers probably innervate the ventricles rather than the sinus node and have an excitability and contractility lowering effect (Machhada et al., 2016). The favorable effect of vagus nerve stimulation to limit the size of ischemic lesion may be due to activation of the fibers originating in the dorsal motor nucleus (Machhada et al., 2015).

Fig. 4. Recording from a Lower Body Negative Pressure Test. Blood pressure and heart rate are recorded at the finger. The figure shows systolic and diastolic values for each beat. Blood pressure is gradually decreasing, heart rate is increasing, at the arrow blood pressure and heart rate start to drop precipitously and the observation is immediately ended by letting the pressure in the box return to atmospheric.

11. Specificity of vagal outflow from central nervous system to peripheral organs

In measuring variability of heart rate, there is the underlying assumption that this is exemplary for the rest of the body and a measure for the condition of the autonomic nervous system as a whole. This question is not about “target specificity” i.e., an anatomical one-on-one relationship between efferent neurons in the medulla and a target somewhere in the periphery. That kind of specificity has been settled (Neuhuber & Berthoud, 2021). No, it is a physiological matter: if the vagus to the heart is active, is it active everywhere? Many publications exist that show (generally weak) correlations between for instance HRV as measure of cardiac vagal outflow and other bodily functions or psychiatric conditions. However, that does not prove the issue at hand, i.e. are the various vagal outflow channels in synchrony?

Relating gut activity to HRV, (Meister et al., 2019) demonstrated that antrum motility of the stomach in freely moving rats showed a modest correlation with fast phasic HRV in baseline conditions. However, this correlation was lost when the stomach was involved in activities like feeding. In humans, deglutition- or swallow-syncope is a known complication of (over-)stimulation of esophageal afferent vagal fibers. This may be due to local constriction of the esophagus, making the passage of food difficult, with extreme wall stretch as a consequence, although it may also occur in people with a normal esophagus (Low & Benarroch, 2008; Mathias & Bannister, 2013). At rest, propulsive colonic motility was seen to go along with increased phasic vagal activity to the heart as evidenced by HRV-analysis (Yuan et al., 2020). These examples demonstrate autonomic intestinal-cardiac relationships. However, the fact that cardiac efferent vagal activity may become engaged in activity of the dorsal motor nucleus, is not proof of a central ‘parasympathetic state’ governing intestine and heart in parallel. Rather may the activity of one center (intestinal control: the dorsal motor nucleus) be spilling over in that of another system (autonomic cardiac efferent control), by the same nucleus or the nucleus ambiguous. In parallel, sympathetic activity to the cardiovascular system may become inhibited (Yuan et al., 2020).
2020). (It must be noted here that the latter authors equated the increased fast beat-to-beat HRV to RSA, without actually referring the observed heart rate variations to respiration). No relation was found between vagal outflows to the bronchi (airway resistance) and to the heart (resting heart period) in humans by (Horvath et al., 1995), when they compared the effects of atropine blockade on those parameters. These are just a few examples that underline the complexity of central autonomic outflow control as recently reviewed by Goldstein (Goldstein, 2021). They also confirm the original Cannon hypothesis that the parasymptomatic system works with high target specificity (Jangi, 2006; Ritz, 2009).

12. The vagus nerve and immunity

The relation between the immune system and central nervous system has long been an enigma. In the 1980’s it became clear that lymph-nodes do have sympathetic innervation (reviewed in (Hori et al., 1995; Madden & Felten, 1995)). Participation of vagal branches was, supposedly, restricted: efferents only to the thymus and afferents from the liver. In more recent years, the vagus has gained more territory in immunology (Baez-Pagan, Delgado-Velez, & Lasalde-Dominici, 2015; Thayer & Sternberg, 2010); it became apparent that there is a cholinergic anti-inflammatory pathway (CAP) where the α7 nicotinic acetylcholine receptors (α7AChR) on macrophages (a special class of immuno-active cells) appear as key-players in the efferent branch (Huston & Tracey, 2011). How exactly these cells receive the signal to start suppressing the cytokine release that accompanies inflammation is not yet settled: the vagus nerve would play a role here. The spleen, the most probable organ to store and mature immune cells, according to most does not have direct parasympathetic innervation. Others contend that vagal activation has an anti-inflammatory effect on immune cells in the spleen via the celiac ganglion and the sympathetic nerves originating there (Pavlov & Tracey, 2012). A recent review, however, casts in doubt the involvement of the vagus nerve in immunological defense: the authors point at the sympathetic nerves, in particular the ones innervating the abdominal organs. I quote from their abstract: “understanding of the effector mechanism is incomplete, but it probably involves a very local action of neurally released noradrenaline on beta2 adrenoceptors on the surface of tissue resident macrophages and other innate immune cells (McAllen, McKinley, & Martelli, 2022).”

By whichever mechanism, electrical vagus nerve stimulation (VNS) has been shown effectively to limit inflammation. For instance, electrical stimulation of the whole vagus bundle in the neck has been applied successfully to reduce the inflammatory response in rheumatoid arthritis (Koopman et al., 2016) or prevent the development of full-blown sepsis in experimental research (Wang, Yin, & Yao, 2016). This leaves open the question how this effect comes about, since whole vagus nerve stimulation activates a bunch of nerves, afferent and efferent, as demonstrated in Table 1. In a 1951 symposium, D. Whitteridge (Wolstenholme, 1953) crusaded in a number of discussions against even the stimulation of mixed afferent nerves, but his verdict on the stimulation of the whole vagus, afferent and efferent, even made it to the literature of his time: it should be a punishable offence (Heymans & Neil, 1958)(p95). More on the issue of VNS will follow below.

13. Stimulating the vagus nerve in therapy

Activation of the vagus nerve by an implanted electrode may bring along many different desirable effects: slowing of the heart in a patient with cardiac failure, intestinal activity to promote peristalsis and digestion, suppression of an immune system running out of control. And these are just some effects on the peripheral effector system. Since the vagus nerve bundle is a mixed nerve (afferent fibers to the central nervous system and efferents to the periphery), what would stimulation of the afferent part do? The message from its afferent fibers can be baroreceptive, chemoreceptive, lung-irritant receptive, satiety, change in the condition of the intestinal intramural milieu (e.g., metabolites or cytokines in the walls of the intestines), etc. However, electrical stimulation generates action potentials in both directions. Antidromic activation of efferent fibers (in which nerve impulses are conducted backwards—i.e., in a direction opposite to the usual one, from the site of stimulation to the central nervous system) may have unexpected central nervous effects, since it may activate other parallel efferent fibers of those neurons, exciting or inhibiting neurons from the same pool. Paradoxical effects of antidromic activation of afferents have been observed as well, like skin vasodilatation due to liberation of a vasoactive polypeptide (Tanaka et al., 2001).

Electrical stimulation of the centrally conducting parts of the cut vagus nerves is exactly what was done in 1938 (Bailey & Bremer, 1938). They were the first to do this while searching for parts of the cerebral cortex that would show altered activity in response to vagal stimulation. Over those areas that are known to be involved in processing of somatic afference, no change in activity was detectable. The only area that reacted was the supraorbital part of the frontal lobe. With present knowledge, every neuroscientist would jump up and consider this a very interesting finding: this area of the cortex is involved in decision-making and in taste, olfaction and emotion (Patesas & Gartner, 2006). Serendipity and the fact that vagus nerve stimulation (VNS) was able to suppress experimentally induced seizures in animals led to, what I would call a “leap of faith-therapy” i.e., implantation of a vagus nerve stimulating electrode in humans to suppress otherwise intractable epileptic seizures, as reviewed in 2000 (Binnie, 2000). Since most cardiac vagal fibers run in the right vagus nerve, the left vagus is chosen for this application, midway in the neck. This therapy is effective in about half of the patients, some months after implantation, and is mostly used as adjunctive to medicinal therapy (Mao et al., 2021) for a recent review. The therapy is not harmless, though: this meta-analysis could not exclude the possibility that some patients had died due to their VNS device. Even though there is now some 20 + years of experience with this therapy, its mechanism of action is still unclear.

The same holds true for other applications, like serious forms of depression (Austelle et al., 2021) or cluster headache (Schuster & Rapoport, 2016). Alternative applications are under development for the same electrode to suppress autoimmune diseases like rheumatoid arthritis (Koopman et al., 2016), lupus, etc. I have had the occasion to sit in on a first stimulation session after electrode implantation in a rheumatoid arthritis-patient. The patient was to be sent home with the stimulator activated, to alleviate her pains over some time. As a physiologist, I was shocked to see how the stimulation was titrated: just turning the settings (pulse duration and amplitude), without any clue of effectivity. Yes, when the stimuli would be too intense (too much current spread to the surroundings) local tingling or hoarseness of voice would be noted. Other than that, one has no idea what the mechanism of action is and how it can be titrated for the various desired effects (some recent attempts at explanation can be found in (Wang et al., 2021)).

Looking around the internet, vagus nerve stimulation seems to have become a panacea. This has intensified since the innervation by the vagus nerve of some small parts of the skin of the outer ear has been rediscovered and put into intended therapeutic use as well, (auricular stimulation) as critically reviewed by (Verma et al., 2021). This stimulation does not require implantation of an electrode with a stimulator and is much easier to apply. However, if there is a physiological effect along the lines of direct vagus stimulation, auricular stimulation is indirect, since it stimulates not just afferent fibers, but also the multitude of fiber types, afferent and efferent, that is involved in invasive VNS.

This mode of application of VNS very unsatisfactory. Of course, it is understandable that one would use a therapeutic method even if its mode of action is unclear, as long as it is effective. But, as with everything vagus, the results are variable and unpredictable. In that vein two recent developments may, in the end, together resolve this issue. On the one hand, electrodes are under development that may, one day, be used in targeted stimulation of even the finest nerve strands
(González-González et al., 2021; Sun et al., 2021), so stimulation may become very specific. On the other hand, physiologists have started recording from individual nerve fibers of the vagus nerve in awake humans (Ottaviani et al., 2020). Until we can with certainty point to the nerves to be stimulated for a specific purpose and then be able to show that this stimulation is indeed activating those nerves, VNS remains like shooting in the dark: sometimes one gets a hit, but not always and not necessarily the one for whom the bullet was intended.

14. Summing up and concluding remarks

The vagus nerve and its possible role in (therapy of) many diseases has stirred interest from many sides. The simplest handle to view its evolutionary background it is shown how control of the many de...
