Autonomic Neuroscience: Basic and Clinical 199 (2016) 48–53

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Review

The strange case of the ear and the heart: The auricular vagus nerve and its influence on cardiac control

Aaron R. Murray [a,1], Lucy Atkinson [a,1], Mohd K. Mahadi [a,b], Susan A. Deuchars [a], Jim Deuchars [a,*]

[a] School of Biomedical Sciences, University of Leeds, Leeds, LS2 9JT, United Kingdom
[b] Faculty of Pharmacy, National University of Malaysia, Kuala Lumpur, Malaysia

ARTICLE INFO

Article history:
Received 4 May 2016
Accepted 20 June 2016

Keywords:
Vagus
Heart
Autonomic
Auricular
Sympathetic
Vagus nerve stimulation

ABSTRACT

The human ear seems an unlikely candidate for therapies aimed at improving cardiac function, but the ear and the heart share a common connection: the vagus nerve. In recent years there has been increasing interest in the auricular branch of the vagus nerve (ABVN), a unique cutaneous subdivision of the vagus distributed to the external ear. Non-invasive electrical stimulation of this nerve through the skin may offer a simple, cost-effective alternative to the established method of vagus nerve stimulation (VNS), which requires a surgical procedure and has generated mixed results in a number of clinical trials for heart failure. This review discusses the available evidence in support of modulating cardiac activity using this strange auricular nerve.

Contents

1. Introduction

The ear has been a site of therapeutic interest for millennia, including reports of women in ancient Egypt using a heated needle to cauterise the skin of the ear as a method of contraception (Gori and Firenzuoli, 2007). In ancient Greece, the physician Hippocrates reported that blood-letting from veins on the posterior surface of the ear could be used as a treatment for sexual dysfunction in men (Round et al., 2013). Chinese traditional medicine, first developed over 3000 years ago, has also placed an emphasis on using manual acupuncture of the ear or auricular acupuncture to influence bodily functions through the concept of 'Qi' and meridians – energy pathways associated with an intrinsic 'life force' which are believed to converge at the level of the ear (He et al., 2012).

The ear is the site of a number of unusual reflexes including the pulmonoauricular reflex, described in three tuberculosis patients with referred pain to the ear (Engel, 1979); the auriculogenital reflex in both male and female cats where mechanical or electrical stimulation of the external ear elicited contraction of muscles around the genitalia (Bradford, 1938); and the auriculouterine reflex, reported in a female patient who felt severe pain in her left ear which coincided with menstruation (Engel, 1979). An auriculocardiac reflex has been identified in a patient who experienced bradycardia following stimulation of the posterior wall of the left external acoustic meatus with a cotton-tipped

* Corresponding author.
E-mail address: J.Deuchars@leeds.ac.uk (J. Deuchars).
[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.autneu.2016.06.004
1566-0702/

ear probe (Thakar et al., 2008). Referred pain to the ear as a result of angina and myocardial infarction has also been described, highlighting the potential connectivity between the ear and the heart (Amirhaeri and Spencer, 2010; Rothwell, 1993).

The basis of these reflexes may be due to variation in the sensitivity of the auricular branch of the vagus nerve (ABVN), which innervates the skin of parts of the ear and the outer ear canal (external acoustic meatus). This branch of the vagus nerve is known as Arnold's nerve after the German anatomist Friedrich Arnold (1803–1890), who first observed that irritation of the posterior wall of the external acoustic meatus elicited coughing in a small number of people (Arnold's Reflex). Subsequent studies have shown that such a response occurs in between 1.7%–4.2% of individuals (Bloustine et al., 1976; Gupta et al., 1986; Tekdemir et al., 1998) and arises due to hypersensitivity of the ABVN (Ryan et al., 2014). This nerve is sometimes known too as the Alderman's nerve, a centuries-old reference to the Aldermen of the City of London and their practice of using rosewater bowls at ceremonial banquets. The banquet attendees were encouraged to place a table napkin moistened with rosewater behind their ears with the belief that this promoted gastric emptying and aided digestion (Treves, 1883).

2. Anatomy of the auricular branch of the vagus nerve

The ABVN is a remnant of the embryonic nerve supplying the first branchial arch (Gupta et al., 1986) and is thought to be derived from nerves supplying the lateral line organ in lower vertebrates such as fish, which use these cutaneous nerves to sense vibrations and movement in the surrounding water (Engel, 1979; Hoagland, 1933). In mammals, the ABVN is distributed to the skin of the ear and external acoustic meatus and consists of somatosensory afferent fibres, with their cell bodies located in the jugular ganglion (DuBois and Foley, 1937). In humans, cadaveric dissection has indicated that the ABVN is the only source of innervation to the cymba concha and further innervates the antihelix, tragus and cavity of the concha (Peuker and Filler, 2002). However, the skin of the ear receives additional sensory innervation from trigeminal afferents (auriculotemporal nerve) and cervical spinal afferents (great auricular nerve and lesser occipital nerve; see Fig. 1), with a variable degree of overlap in the respective dermatomes (Peuker and Filler, 2002).

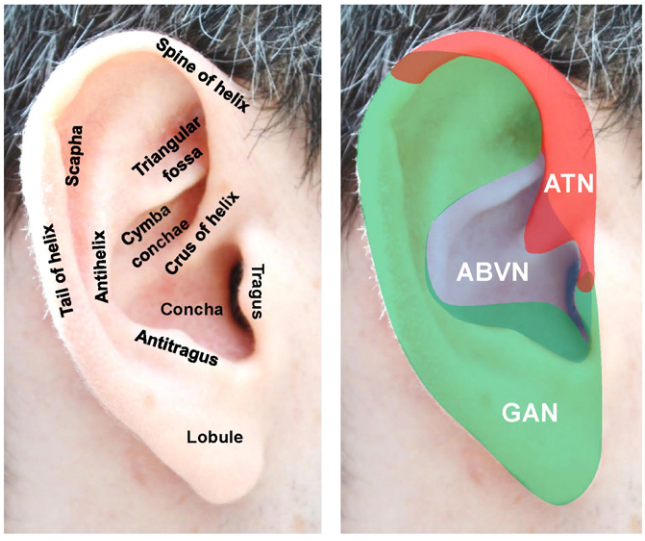

Fig. 1. Anatomical landmarks and cutaneous innervation of the external ear. Three nerves contribute to the cutaneous innervation of the lateral aspect of the ear: the auricular branch of the vagus nerve (ABVN), the auriculotemporal nerve (ATN) and the great auricular nerve (GAN). There is a variable degree of overlap in the distribution of these cutaneous nerves.

How can stimulation of a small nerve in the ear elicit such a wide range of physiological responses? The answer becomes clearer when the vagus nerve is considered in its entirety. Regarded as the main parasympathetic output of the autonomic nervous system, the vagus nerve has an extensive distribution throughout the thorax and abdomen. In its role as the "great wandering protector" of the body, it relays sensory information about the state of the body's internal organs to the central nervous system via afferent fibres which make up 80% of the nerve (Foley and DuBois, 1937). Upon exiting the cranium via the jugular foramen, the vagus provides innervation to the soft palate, pharynx and muscles of the larynx prior to entering the thorax (Berthoud and Neuhuber, 2000). At this point, the 'wandering' nature of the vagus becomes apparent through its complex distribution to the heart, lungs, liver, adrenal medulla and the gastrointestinal tract up to the splenic flexure of the colon (Clancy et al., 2013). The remaining 20% of vagus nerve fibres are efferent fibres originating from the brainstem which provide parasympathetic control of the viscera and heart (Foley and DuBois, 1937).

The large number of afferent fibres in the vagus has led to it being investigated as a therapeutic pathway for influencing brain activity by means of electrical stimulation. In humans, vagus nerve stimulation (VNS) can be achieved by implanting an electrical stimulator under the skin of the chest which stimulates the cervical vagus nerve via a bipolar lead wrapped around the nerve. VNS was developed in the 1980s in patients with intractable epilepsy, is approved for the treatment of refractory epilepsy and depression and has a well-established safety profile in these patients (Groves and Brown, 2005; Morris and Mueller, 1999; O'Reardon et al., 2006).

Given the critical role of the vagus nerve in providing parasympathetic innervation to the heart, there has been interest in using VNS to modulate cardiac function. In animals, electrical stimulation of the cervical vagus nerve has been shown to evoke cardiovascular effects, for example by lowering the ventricular fibrillation threshold (Brack et al., 2013). Moreover, VNS is known to reduce incidence of ventricular arrhythmias and mortality during ischemia (Brack et al., 2013) and prevent sudden cardiac death in dogs with myocardial infarction (Vanoli et al., 1991). VNS has also been investigated in animal models of chronic heart failure, a condition characterised by a sustained increase in sympathetic drive and a concurrent withdrawal of parasympathetic activity (Triposkiadis et al., 2009). A sustained improvement in cardiac function and heart failure symptoms has been demonstrated as a result of VNS (Hamann et al., 2013; Kusunose et al., 2014; Li et al., 2004; Sabbah et al., 2011; Zhang et al., 2009).

The results of these animal studies combined with the well-established safety profile of VNS have encouraged investigation into the feasibility and tolerability of VNS in heart failure patients. Preliminary results using VNS showed promise and stimulation of the right cervical vagus nerve with pulses synchronised to the cardiac cycle improved NYHA class, quality of life scores and left ventricular end-systolic volume (Schwartz et al., 2008). Larger studies subsequently showed VNS was associated with a significant improvement in cardiac function, quality of life scores and exercise performance (De Ferrari et al., 2011; Premchand et al., 2014).

However, a recent larger clinical trial concluded that 6 months of VNS failed to have a significant effect on cardiac remodelling and cardiac function in heart failure patients. Nevertheless, the study did show an improvement in quality of life measures and NYHA classification (Zannad et al., 2015). A subsequent international multi-centre clinical trial using VNS on heart failure patients to assess whether VNS increases the time to first event defined by all-cause mortality or unplanned heart failure hospitalization was discontinued due to a statistical futility in this primary efficacy endpoint (Gold et al., 2016). Although the safety profile of VNS is recognised, the technique requires surgical implantation of the electrodes and a subcutaneous battery pack, with an increased risk of post-operative complications such as infection (Elliott et al., 2011). Other acute side-effects of VNS can include neck pain,