

Neuroprotection: yes, ear CAN!

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Abstract

Increasingly efficient but aggressive therapeutics are about to spread in the field of neuroprotection. Nevertheless, most of them require technological and scarce environment, limiting the number of included patients. The patient's ears, on the contrary, are available and easy to reach, which make them interesting tools to potentiate the state-of-the-art treatments. Concurrently, ears and brains are naturally connected through the brainstem. Therefore, stimulation of the ears can modulate the Central Autonomic Network (CAN) (notably through vagus nerve stimulation) and bring homeostasis back. Moreover, Auricular Neuromodulation has been successfully used to relieve pain in battlefield, supporting its ability to win the race against time for neuroprotection.

Abbreviations and symbols: AN: Auricular Neuromodulation; ANS: Autonomous Nervous System; CAN: Central Autonomic System; HRT: Heart Rate Variability; rTMS : repetitive Transcranial Magnetic Stimulation; SCP: Superficial Cervical Plexus; US: United States; V: Trigeminal nerve; VNS: Vagus Nerve Stimulation; tVNS: transcutaneous Vagus Nerve Stimulation; X: Vagus nerve.

Introduction

Despite tremendous advances, two limiting factors still partially stand in the way of neuroprotection: the ability to deliver therapeutics at the right place and at the right time!

Therefore, the ideal neuroprotective strategy should be:

- 1) Unique, suitable for any neurological disease and for any patient regardless of its age or gender (reducing the time spent to make the diagnosis, mandatory for the drug to be « at the right place »),
- 2) Fast acting, designed for acute as well as chronic disorders, (for the drug to be « at the right time »)
- 3) Easy to reach (for optimizing medical care).

Nowadays, Autonomous Nervous System (ANS) disturbances are described in most acute neurological diseases (Cerebrovascular diseases [1,2], Traumatic Brain Injury [3]) as well as chronic ones (Epilepsy and Tourette syndrome [4], Neurodegenerative diseases [5], Neurodevelopmental diseases like Autism Spectrum Disorders [6]).

Concurrently, ANS has earned stripes. It is no longer defined in terms of its peripheral connections (the sympathetic and the parasympathetic arms). From now on, emphasis is laid upon the central components of ANS. It is named CAN for Central Autonomic Network and includes the insular cortex, the amygdala, the hypothalamus, the periaqueductal gray matter, the parabrachial complex, the nucleus of the tractus solitarius (one of the nuclei of the dorsal vagal complex) and the ventrolateral medulla [3,7,8].

Moreover, severe autonomic dysfunction (often measured by a decrease of Heart Rate Variability, HRV) is related to an unfavorable functional outcome [9-12]. As a consequence, up-regulation of HRV through Vagus Nerve Stimulation (VNS) could end up with

neuroprotection [13,14]. In a recent paper, to be published this november, a percutaneous mastoid electrical stimulator used within 3 days after acute ischemic stroke was able to alleviate HRV and reduce mortality [15].

Among non-invasive VNS techniques, transcutaneous Vagus Nerve Stimulation (tVNS), the stimulation of the concha of the outer ear (the only superficial area of the body supplied by the vagus nerve) is one of the most attractive options [16-21].

More broadly, Auricular Neuromodulation (AN) fulfills the prerequisites for ideal neuroprotection

1) AN allows to « be at the right place »

Auricular Neuromodulation is able to stimulate CAN [22] thanks to the vagus nerve (X), the trigeminal nerve (V) and the superficial cervical plexus (SCP) [23]. This technique is efficient for a wide range of neurological disorders (for a review, [24]).

Likewise brain hubs have been discovered, there might be « ear hubs » to unravel [24], able to easily stimulate brain hubs, therefore providing neuroprotection for potentially any neurological disease [25,26]. Recent findings support this hypothesis : AN was proven to be able to modulate GABAergic transmission [16]. Coincidentally, operational hub cells are known to be GABAergic neurons [27]. Furthermore, a previous anatomical report had confirmed that the Nucleus Tractus Solitarius was linked via multisynaptic relays to the hippocampus [28]. At last, a few years later, evidences concluded in the presence of hub neurons in the hippocampus [29].

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Not only Auricular Neuromodulation can mediate a neuroprotective action owing to its inherent properties but also it could allow a “synergistic effect” with more technically advanced therapeutics like rTMS [30]. Therefore, the outcome of the patient is likely to improve, more as AN happens to be a very fast acting treatment.

2) AN allows to « be at the right time »

Because AN effect is mediated by myelinated nerves (X, V and SCP), it proceeds rapidly, faster than most drugs and require only basic and affordable material (needles, handheld devices).

Therefore, AN could be realized as soon as a neurological symptom appears, regardless of the setting. Indeed, US Army was the first to test this technique with success. Until now, more than 5 millions of dollars have been spent to teach soldiers how to puncture up to 5 needles on the ear in order to deal with any kind of pain (amputation, bullet wounds...) occurring during war. This was called « Battlefield Analgesia » or « Battlefield Acupuncture » [31,32]. Battlefield Acupuncture was so efficient that it expanded to hospital emergency departments, relieving within minutes acute and/or intense pain [33,34]. Concurrently, a pilot study, using magnetic pellet instead of needles, supported Battlefield Acupuncture for preventing pain in neonates [35].

Nevertheless, contrary to Battlefield Acupuncture, the protocol of « Auricular Neuroprotection » is not set yet and must be designed. Regarding this issue, the choice of the ear points is of the greatest importance [36]. The next step regarding neuroprotection, would consist in teaching AN to medical and paramedical staff, experienced in resuscitation and intensive care. AN would be complementary to the more « aggressive » therapeutic options (reperfusion, endosomes, stem cell therapy...), aiming at optimizing patients’ prognosis and decreasing side effects.

Hence, it is urgent to develop clinical trials assessing the contribution of AN in addition to other neuroprotective treatments. The US Army, which used to contribute to the democratization of computers, has been using Auricular Neuromodulation for roughly 10 years. « I introduced Battlefield acupuncture at the bedside of these heroic patients, and the demands from both patients, families, and physicians skyrocketed » says Dr Richard Niemtow [32]. Maybe in twenty or fifty years from now, Auricular Neuromodulation will have become a routine in neuroprotection. « Yes, we CAN! » Can’t we?

Autorship and contributorship

I am the only author of this manuscript (Dr Claire-Marie RANGON).

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