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Advances in Electrostimulation Therapies

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Preface

Electroceuticals is a term that has recently come into use and encompasses the rapidly growing fields of bioelectrical and bioelectronics medicine. In broad and general terms, electroceuticals covers the therapeutic use of electrical stimulation to influence and modify biological functions or pathological processes in the body. Strictly speaking, this field is not new. Electrical stimulation has been used over the last 50 years for therapeutic benefits. For example, electroconvulsive therapy has been successfully employed for decades to treat pharmacologically resistant depression. However, over the last 20 years, there has been an exponential rise in research activity focused on electroceuticals, and exciting new areas of discovery and development have emerged which may offer alternatives to the traditional pharmaceutical options. The increasing sophistication and miniaturization of technology coupled with rapid advances in understanding of the function of electrical pathways in the body has made it increasingly feasible to modify electrical pathways for therapeutic gain.

This has also been reflected in the increased interest that research funding bodies such as the National Institute of Health (NIH) in the USA and pharmaceutical companies like GlaxoSmithKline (GSK) have taken in this area. The NIH has established a US$248 million fund to map the electrical wiring of the body and advance the development of new therapeutics. Similar efforts have been initiated by GSK.[1] Other initiatives like the NIH-funded human connectome project also promise to unravel the structural and functional connectivity of the human brain in health and disease.[2]

In this book, we present areas where electroceuticals research has made exciting progress toward therapy development. These include clinical neural implants such as cochlear implants to restore hearing, deep brain stimulators to treat movement disorders, and stimulation of the pharynx and of peripheral nerves to assist in dysphagia and gait disorders.

More recent varieties of electroceuticals include the electrical stimulation of the vagus nerve to modulate the immune system in order to provide relief from rheumatoid arthritis, prevent epileptic seizures, treat heart failure, aid recovery from brain trauma, and treat inflammatory bowel disease and gut motility disorders. Equally exciting is the potential that electroceuticals may enhance memory and consciousness.

Electroceuticals is a broad and rapidly growing field, and it is not possible to cover all the progress that is being made. However, we believe that this publication will give the reader new insights into the progress that has been made in this field. Each chapter in this book has been written by experts with an international reputation in their specialty who discuss the development of electroceuticals in their disease areas. They have included discussion on the historical background, research developments, current uses, and future prospects.

The regulatory approval process is of course an important consideration for all therapy development. However, I have chosen not to include chapters on the regulatory process as it varies according to jurisdiction and it would not be possible to cover all the jurisdictions of potential readers of this book.

Despite the rapid progress that has already been made, we stand at the dawn of a new era that will surely see huge developments over the coming decades, not only in treatments of diseases but also in enhancing human function.

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About the Editor

Arshad Majid is a Professor of Cerebrovascular Neurology and Consultant Neurologist at the University of Sheffield and the Royal Hallamshire Hospital. Professor Majid graduated in Medicine from the University of Glasgow, Scotland. He trained in Neurology at the University of Pennsylvania and did fellowship training in Stroke Research at Washington University in St. Louis. He did additional fellowship training in Endovascular Surgical Neuroradiology at the Medical College of Wisconsin. He then served as the founding Director of the Division of Cerebrovascular Diseases at Michigan State University and was also the founding Medical Director of the William and Claire Dart Stroke Center at Sparrow Health System in Lansing, Michigan. He has published extensively in international peer-reviewed journals and presented at national and international meetings. His research has been funded by the NIH, the American Heart Association, the NIHR (UK), and the industry.

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Chapter 1
The Use of Electroceuticals and Neuromodulation in the Treatment of Migraine and Other Headaches

Sarah Miller and Manjit S. Matharu

Abstract Over recent years there has been increasing interest in the role of neurostimulation in the treatment of headache disorders. Currently both peripheral and central neuromodulation devices are available although evidence to support their use is still limited. Both non-invasive and invasive devices can be used for neurostimulation. Non-invasive peripheral stimulation options include supra-orbital stimulation (Cefaly® device) and vagal nerve stimulation (gammaCore® device), while invasive peripheral stimulation options include occipital nerve stimulation and sphenopalatine ganglion stimulation. Non-invasive central neurostimulation option involves single pulse transcranial magnetic stimulation (SpringTMS® device), while invasive central neurostimulation can be carried out using ventral tegmental area deep brain stimulation. Neurostimulation therapies offer a promising approach to otherwise medically intractable or difficult to treat headache disorders with each device having specific roles within the treatment pathway.

Keywords Electroceuticals • Nuromodulationl • Migraine • Headaches

Introduction

Primary headache conditions are benign, reoccurring headaches not caused by any underlying structural issue or disease. The primary headaches are subdivided into phenotypes based on the International Classification of Headache Disorders (ICHD-III beta) [1]. The main divisions are migraine and the trigeminal autonomic cephalalgias (TACs). Migraine is a recurrent headache disorder manifesting in attacks of pain lasting between 4 and 72 h, which is accompanied by nausea, vomiting, light and noise sensitivity and aggravation of the pain with movement. The TACs are a group of disorders characterised by unilateral head pain occurring in association

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with prominent ipsilateral cranial autonomic features. The TACs include cluster headache, paroxysmal hemicrania, hemicrania continua and short-lasting unilateral neuralgiform headache attacks, which is further subdivided into SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and SUNA (short-lasting unilateral neuralgiform headache attacks with autonomic symptoms). The most common primary headache is migraine with an estimated 15% of the population affected [2]. The TACs are less common with estimated prevalence of cluster headache of 1 in 500 [3], of paroxysmal hemicrania around 0.5 per 1000 [4] and that of hemicrania continua and SUNCT/SUNA not well defined but thought to be similar to that of paroxysmal hemicrania [4]. The clinical features, epidemiology and first-line treatment options are summarised in Table 1.1.

The above primary headache conditions can be classified by their frequency into either episodic or chronic forms. Chronic migraine is defined as a headache occurring on 15 or more days of the month (of which eight or more are migrainous) for a period of over 3 months. Chronic TACs are diagnosed when patients go a year without remission periods or with remission periods lasting less than 1 month [1]. Chronic headache is a global health issue affecting up to 4% of the population [5], with chronic migraine or cluster headache forming the majority of chronic headaches seen in neurology units. The estimated prevalence of chronic migraine is 2% and chronic cluster headache 0.02% [6]. Patients may have headaches that are chronic from onset or evolve from an episodic form.

Although advances in the management of headache disorders means that the majority can be managed with medical treatments, a significant minority will not tolerate or prove intractable to available preventative pharmacological treatments. Neurostimulation techniques with peripheral and central targets appear to offer a promising approach to treating such patients. Devices allowing acute treatment of attacks may be useful to those unable to use or who overuse acute medications such as triptans. The peripheral targets used include the occipital nerve, the supra-orbital nerves, the sphenopalatine ganglion and the vagus nerve. Current central targets are the ventral tegmental area and the cortex. In this chapter, the main focus is on the treatment of chronic migraine and chronic cluster headache as this is where the bulk of literature and experience lies. Some reference will be made to the treatment of episodic migraine and cluster headache where relevant.

Pathophysiology of Primary Headache Conditions

Migraine

Migraine is a complex neurological disorder that affects multiple cortical, subcortical and brainstem regions that regulate the autonomic, affective, cognitive and sensory functions. The pathophysiology of the condition involves different neural networks and pathways interacting together to generate the clinical features of migraine. The main pathways and mechanisms involved in migraine generation include (Fig. 1.1):

Table 1.1 Clinical features of the primary headache disorders

	Migraine	Cluster headache	Paroxysmal hemicrania	SUNCT/SUNA	Hemicrania continua
Frequency in general population	15% (2% chronic)	0.2%	Rare	Rare	Rare
Sex ratio	Female > male	Male > Female	Female = Male	Male > Female	Female > Male
Pain:					
Description	Throbbing, aching, squeezing	Stabbing, boring	Stabbing, boring, throbbing	Sharp, stabbing, neuralgiform	Background pain: dull, heavy Exacerbations: throbbing, aching, squeezing
Severity	Moderate to severe	Severe, excruciating	Severe, excruciating	Severe, excruciating	Mild to moderate background pain with severe exacerbations
Laterality	Unilateral or bilateral	Unilateral	Unilateral	Unilateral	Unilateral
Attack frequency	Variable	1 to 8 attacks a day	5–40 attacks a day	3–200 attacks a day	Continuous pain
Attack duration	Hours	15–180 min	2–30 min	5–240 s	Continuous pain
Periodicity	–	Circadian and circannual ++	Circadian and circannual +/–	–	–
Autonomic features[a]	Sometimes, mild	Yes	Yes	Yes	Yes, with exacerbations
Migrainous features[b]	Yes	Yes, may be mild	Yes, may be mild	Rare	Yes
Triggers					
Alcohol	Yes	Yes	No	No	No
Cutaneous touch	No	No	No	Yes	No
Indometacin response	None	None	Complete resolution	None	Complete resolution
Abortive treatment	Oral triptan, NSAID	Subcutaneous Sumatriptan, Oxygen	Nil	Nil	Nil
First-line prophylactic	Beta-Blockers, tricyclic antidepressant, topiramate	Verapamil, lithium, topiramate	Indometacin	Lamotrigine, oxcarbazepine	Indometacin

NSAID non-steroidal anti-inflammatory drugs, *SUNA* short-lasting unilateral neuralgiform headache attacks with autonomic features, *SUNCT* short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

[a]Autonomic features: One or more of ptosis, lacrimation, conjunctival injection, facial redness/sweating, eyelid/facial swelling, nasal stuffiness, rhinorrhea

[b]Migrainous features: One or more of nausea and/or vomiting, photophobia, phonophobia