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AIM AND SCOPE

World Journal of Neurology (*World J Neurol*, *WJN*, online ISSN 2218-6212, DOI: 10.5316) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJN covers topics concerning neuro-oncology, electroneurophysiology, cerebrovascular diseases, epilepsy, cognitive impairment, myopathy and peripheral neuropathy, degenerative diseases, infectious diseases, demyelinating diseases, immunological diseases, genetic/metabolic diseases, affective disorders, headaches, sleep disorders, interventional neuroradiology, minimally invasive therapy, rehabilitation, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of neurological diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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EDITORIAL

Challenge of the translational neuroscience

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Abstract

The development of Neurosciences in the last few years has changed a set of paradigms in the production of knowledge, from which new scenarios have arisen in the understanding of the structure and function of the human nervous system, as well as in some of the most relevant diseases involved. Nonetheless, the impact of all the scientific information on this topic has played a limited role in the proposals in the diagnostic, therapeutic, rehabilitation and social reintegration fields, when the effect on the daily life of patients that have a neurological impairment is considered. Thus, the emergence of translational science is an alternative for a more direct and pragmatic link that allows the connection between basic research and applied research, and in the short term will achieve results that can be promoted in the communities. In addition, this process involves an interaction with technological development and transfer following a global knowledge management model. Every discipline in the neurological sciences field poses different critical challenges to tend to the new epidemiologic profiles. emerging in areas such as neurodevelopment disturbances found in the pediatric population, trauma and addictions in the young, as well as neurodegenerative diseases in older adults. This model reviews the demands from society, expecting more compelling results from the scientific community, particularly in creating strategies that actually change the natural course of neurologic diseases from the bench to the bedside.

Key words: Medical research; Neurology; Neurosurgery; Neuroscience education; Neuroethics; Translational medicine

Core tip: The society of knowledge has expanded with information produced all over the world. But unfortunately, only a small part of such knowledge has had an impact on decision-making pertaining health, and on the ability to solve specific problems in a given population. Translational Neurosciences represent an innovative proposal for a direct line between basic research, applied research, technology transfer and knowledge management for the resolution of a specific problem in the neurological sciences, either in diagnosis, therapy, rehabilitation or social integration. This design requires commitment with education and training of human resources in Neurosciences from a proactive and innovative viewpoint.

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INTRODUCTION

The control of certain emerging diseases and proposals for prevention has been fostered by the growth of science and technology. New innovative strategies have been devised that have favorably changed the worldwide standards of life quality and life expectancy.

However, the creation of new information does not necessarily mean that scientific knowledge is duly applied at every public health level. The society of knowledge has expanded with information produced all over the world, but unfortunately, only a small part of such knowledge has an impact on decision-making pertaining health, and on the ability to solve specific problems in a given population.

The gap between the production of knowledge and its application in daily life and health issues in the communities is today a major challenge[1,2].

TRANSLATIONAL MEDICINE

One of the best methodological strategies to rethink the paradigm of the production and application of knowledge is found on translational science. It comes forth under the promise of change and a direct short-term impact on the interaction between knowledge and problem resolution. For pragmatic purposes in health sciences this precept is applicable to the concept of Translational Medicine[3].

A crucial fact from its origin is that it arises from the same demand of the so called translational epidemiology, which has been profiled as an emerging condition that supports. That is due to the pertinence of its origin, to try get the different fields of biomedical research to have an impact on public health at the shortest possible term[4].

This protocol makes it more feasible to allow for the transition of basic research into action and resources that are specifically an answer to clinical needs in a more timely and specific way.

One of the most accepted definitions states that it is a process by which the scientific research discoveries are transformed by clinical projects that allow for new treatments promote diagnosis, treatment and disease prevention in the short term. In the scientific literature it is identified as a collection of monographs that are described in a format called "from the bench to the bedside".

This proposal is put forth as bidirectional, since multidisciplinary work is a commitment from the members of the basic research team and the clinical investigators, and it also allows to rethink the prevailing problems in clinical work that need support from basic science. In other words, the proposal strengthens competences and promotes resolution of concrete problems punctually and specifically, under a strategy of multidisciplinary leadership and teamwork.

The way of thinking is linear, dynamic, bidirectional, with innovation in the pivotal points and the traditional scope of biomedical research, where the commitment lies on the idea that knowledge coming from a reality must go back to it and transform it, beyond a mere description under the perspective of scientific rhetoric[3,4].

Its field of action is broad, since on one hand it requires, due to its own nature, an operative link with technology transfer, creation of patents, promotion of intellectual property and even entrepreneurship. On the other hand, it requires an accurate link with knowledge management and the impact on management guidelines and decision-making in a specific problem in the realm of public health.

TRANSLATIONAL PERSPECTIVE IN NEUROSCIENCE

Basic neurosciences have had an extraordinary progress in the last 30 years which has modified the frontiers of knowledge and has changed paradigms in neurogenesis, molecular structure, genetics, network functions and specific circuits. This has led to better understanding of basic science and neural pathophysiology and neuropathology, having a high impact on clinical neurology and cognitive neurosciences. In spite of all that, the molecular mechanisms underlying the different diseases and their respective treatment have not been totally elucidated, therefore, many questions remain unanswered in every branch of the knowledge[5].

In view of these events, societies and some political leaders have questioned the fact that although brain research has been consistently supported, compelling advances have not been obtained in the treatment or prevention of the most disabling cerebral diseases in human beings[6,7].

Aside from the complexity in the analysis of the human brain, transfer of neuroscientific knowledge to the biosanitary field has not been easy. This is related in terms not only of primary research and its application, but also including some other factors such as the so called T2 translational research that puts forth limitations and barriers so that the relevant products of basic and clinical research can move on to be applied in health systems at short term, due to feasibility and cost-benefit implementation difficulties[8].

This feature has a direct impact on the creation of new treatment strategies for neurologic diseases of every sort, which are the ones that account for a high rate of disability. Also have an effect on people's independence and the consequent social and economic impact on public health systems.

This scenario in Neurosciences is an overt example where we find an imperative need to transfer knowledge to the bio-health sector, which has led the Health

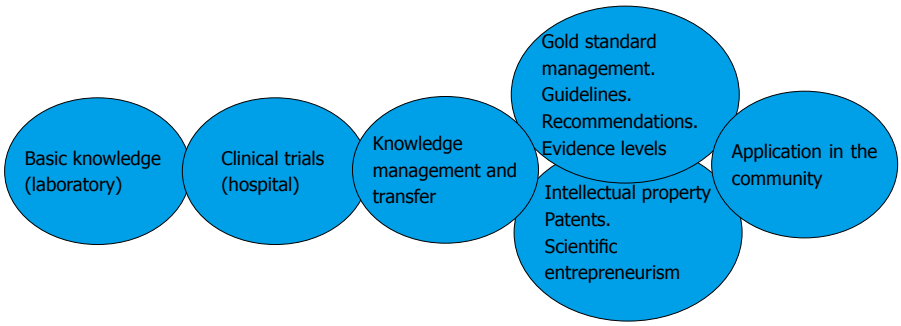

Figure 1 Lineal representation that links the different phases in the production and application of knowledge from the translational perspective.

Institutes - National Institutes of Health, INH- to redirect the funds from research lines to advanced projects in the field of Translational research, in view of a predictable social and public health impact[9].

Consequently, the scientific world has undertaken a series of steps for the creation of a more integrative multidisciplinary strategy between Basic and Clinical Neuroscience.

Ever since the decade of the brain[10], and up to the implementation of more recent study projects such as the BRAIN project[11], and the recently created project of the human connectome[12], every effort in the different scientific communities has the goal of conducting research to discern the map of the human brain and its implications for disease in different clinical areas, such as Neurology, Neurosurgery, Neuropsychopathology and Psychiatry. However, the real challenge must be to discuss the goals with the greatest reach that will be able to link the different research levels with concrete applications at short term, that can actually have direct impact on health and that also promote public healthcare and prevention policies[13].

In the case of Neurosciences, the demand is for almost immediate application. First, due to the large amount of scientific information that is produced in the field. Second, because of the still perceptible distance between research and its effects, since it is considered that such impact has not been big enough to change the epidemiology of diseases that involve the human nervous system and that are a challenge and an emergency in worldwide public health[14].

Translational Neurosciences represent a new proposal for a direct line between basic research, applied research, technology transfer and knowledge management for the resolution of a specific problem in the area of neurological sciences, either in diagnosis, therapy, rehabilitation or social integration (Figure 1).

This feature gives a reference framework according to world trends, but also sets the limits and scope concerning specific topics in basic science and clinical work. Also, this design requires commitment for education and training of human resources in this topic from a proactive and innovative viewpoint. The model pursues not only to be involved in the transformative practice offered by translational science, but also to promote proactive mechanisms of knowledge management that can support the algorithms in the decision making. Also, other process around health and public policies at a global level with more compelling scientific strength, but supported on local needs.

TRANSLATIONAL IMPACT IN TIME

Some of the limitations of this process are the so called gaps or death valleys, where time sequence plays a crucial role. They involve extended laboratory research time periods due to their own nature, with the consequent loss of continuity and validity on a specific subject of knowledge to be applied in clinical settings (Long periods between biomedical research phases I-II-III, approval delays, flaws in research product feasibility and availability, questions in cost-benefit balance). Additionally, it must be considered that regulatory criteria and scientific rigor itself can occasionally reduce the implementation of new projects and their clinical application, in spite of having been successful and promising in the research laboratory.

Under emerging conditions, these time periods are shortened by common sense and the existing social pressure under certain circumstances such as epidemics. Or due to the individual decision of patients about using experimental therapies at their own risk even if they are still not approved. This is particularly obvious in case of diseases for which there are no curative treatment options, as happens in certain neurodegenerative diseases[5].

Nevertheless, this condition must not misrepresent the fundamental premise in Bioethics and now Neuroethics by assuming that the viability of the translational process to apply knowledge at short term could compromise the values, rights and responsibilities in protecting health and integrity of patients as a primary endpoint[15,16].

CHALLENGES IN NEUROSCIENCES

The World Health Organization (WHO) has proposed studies that have led to public policies on global health, based on surveys and epidemiological analysis in the area of neurological sciences. Agreements among different institutions, have integrated a proposal concerning

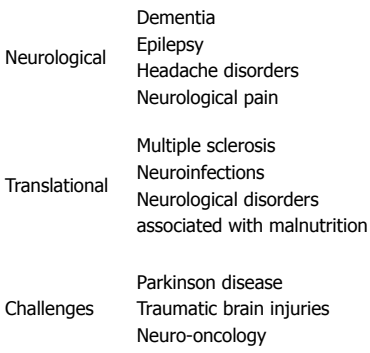

Figure 2 The most relevant challenges for global health in neurosciences for the future years.

neurological disorders as a public health challenge[1].

Under the basic public health principles and knowledge management, a very specific proposal has been postulated involving the most relevant challenges for global health, not only for today but also with future projection under different schemes for years to come: (Figure 2).

In this illustrative outline a methodological design is set forward, contemplating basic public health precepts, such as global health, community health, prevention, monitoring, epidemiologic surveillance and social conditions to attain equitable health.

According to this project, decisions for primary prevention (measures to avoid the onset of disease), secondary prevention (accurate and timely diagnosis, appropriate treatment and management of risk factors), and tertiary prevention (rehabilitation, palliative care, treatment for complications, patient and caretaker education, self-help groups, reducing stigma and discrimination and fostering social integration) are duly stipulated[1,17].

If we analyze the new challenges for Neurosciences as a projection into the future, a new position and a new strategy are required, so that in a practical way there can be a direct reflection on the epidemiological framework, under a translational format[18]. An example is the case of the comparative analysis applied to the use of a helmet and its effect on consequences of traumatic brain injury as evidence[19].

On the other hand, it is also pertinent that the proposals to solve these problems should have a long term and obvious impact on functional quality and the quality of life of subjects who have neurological disorders. Consequently, the translational challenges of the new research projects in Neurosciences must also find a way to have a favorable impact or effect on the disability and physical limitations, cognitive sequelae, behavior sequelae, communication and daily life activities as well as psychosocial issues in patients. All, within a global social context and under a scheme that is associated with the commitment of preserving health as a crucial component of the individuals universal rights.

CONCLUSION

It is crucial that under this vision of things new educational schemes that strengthen the training of human resources on basic neurosciences and all neurological sciences should be created, with a clear commitment of collaboration in "translational teams". In such a way that they are able to update the core curricula (undergraduate and postgraduate), continuing medical education, accreditation and certification; the creation of international networks, the integration of non-medical professionals, the rational use of new technology and consideration of the projective public healthcare and emerging conditions.

Translational Neuroscience must face the challenge of growing from methodological and technological innovation to the production of new knowledge through basic and applied research, promoting discipline and leadership. The exchange and optimization of research work must consider knowledge and transfer management as a priority, for the benefit of community health.

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FRONTIER

Medicine in the future - with subspecialists in medullary neurology and brain dentistry

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Abstract

The solitary tract nucleus of the medulla with its limited watershed vascular capacity may occasionally be the focus of transient ischemia caused by the increased metabolic demands associated with frequent and intense neuronal stimulation from other organs and other parts of the brain. Case reports have suggested that these ischemic changes may sometimes result in the initiation of intense autonomic discharges, which can occasionally be fatal. Therapeutic interventions for the medulla oblongata are hampered by its limited accessibility. Systemically administered pharmaceuticals may have some usefulness in future years. Previous experience with vagus nerve stimulation in the treatment of epilepsy suggests that it may have some usefulness in stabilizing medullary autonomic discharges. Computerized electronic stimulation of other cranial nerves may be helpful as well, especially the chorda tympani nerve, and may be most easily accomplished from implanted dental appliances, especially molar modules, transmitting signals *via* secondary transmitters procedurally placed on cranial nerves. Future technology may enable wireless signaling from the implanted dental appliance to the secondary transmitter placed at the nerve site. By the year 2050 subspecialists in medullary neurology and brain dentistry may use computerized electronic stimulation of cranial nerves to prevent sudden unexpected death and treat "chest pain from the brain".

Key words: Solitary tract nucleus; Ischemic autonomic umbra; Medulla oblongata; Molar module; Chorda tympani nerve; Medullary brain lesion; Medullary neurology; Chest pain from the brain; Sudden unexpected death; Brain dentistry; Vagus nerve stimulation

Core tip: Medical investigators in the 21st century have reported numerous cases in which the presence of a small medullary brain lesion was associated with sudden unexpected death. Many such medullary lesions have otherwise produced only minor clinical symptoms and have in themselves been previously considered relatively harmless. Many victims have been considered healthy prior to sudden death, and the medullary brain lesions were incidental discoveries at autopsy, with no other causes of death identified.

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MEDULLARY NEUROLOGY

Medullary neurology, as described here, is a branch of medical science concerned with the medulla oblongata and its disorders. The term may bring to mind the work of several 19th century neurologists, such as Wallenberg, who described stroke syndromes resulting from occlusive vascular disease affecting different parts of the vertebro-basilar artery system and sometimes related to syphilis. Some of those infarctions involved autonomic fibers located in the medulla oblongata, and resulted in focal autonomic deficits involving the face. Also described in that era was medullary brain irritation resulting in fulminant systemic autonomic phenomena affecting thoracic organs. In 1861 Brown-Séquard[1] discussed his own clinical observations in the context of then recent laboratory reports by physiologists that "sudden irritation of the medulla oblongata often produces arrest of the heart's action", but that this can be blocked by sectioning of the vagus nerve.

The concept of "occlusive cerebrovascular disease as a cause of strokes" subsequently flourished in clinical practice, and the names of those 19th century investigators remain in today's medical lexicon as eponyms for specific neurological deficits. But the concept of "medullary irritation as a cause of fulminant systemic autonomic phenomena" smoldered and never caught fire. Certainly when someone drops dead unexpectedly in the year 2015, the last thing that anyone considers as a possible cause of death is a cardiac arrest resulting from medullary irritation from a small medullary brain lesion in the absence of hemorrhage or mass effect.

That may be about to change - not because medullary brain lesions, as traditionally defined, are so common, but because our traditional clinical concepts regarding ischemic lesion formation in the brain medulla fail to acknowledge its dynamic interactions with the heart, other organs, and other parts of the brain and particularly that those interactions in themselves may occasionally initiate the formation of focal ischemic medullary brain lesions by exciting some areas of the medulla beyond the fixed capacity of their watershed vasculature to supply metabolic nutrients.

SUDDEN DEATH

Medical investigators in the 21st century have reported numerous cases in which the presence of a small medullary brain lesion was associated with sudden unexpected death. Many such medullary lesions have otherwise produced only minor symptoms and have in themselves been previously considered relatively harmless. Among the most common, and pathologically benign, were those caused by small infarctions, sometimes associated with diabetes, hypertension, and sleep apnea. But a wide variety of infectious and inflammatory illnesses, as well as multiple sclerosis, have been discovered involving the brain medulla in the setting of sudden unexpected death[2]. Excluded, however, from this phenomenon were large brainstem hemorrhages, infarctions, and compressive lesions, all otherwise long known to cause sudden death.

Clinical cases of sudden unexpected death related to medullary brain lesions, specifically following cardiac arrest[3-7] or following respiratory arrest[8-17] have been reported in approximately equal numbers[2], and all age groups have been involved[2]. In many descriptions of sudden unexpected death related to medullary brain lesions the victims had been considered healthy prior to death, and the medullary brain lesions were incidental discoveries at autopsy, with no other causes of death identified. Pathological findings suggest that sudden unexpected death related to medullary brain lesions is most commonly related to lesions which include specific anatomical regions within the medulla: the solitary tract nucleus in all age groups[10,18,19], and several additional medullary areas specifically in infants[20-22]. The solitary tract nucleus is a medullary autonomic recipient of sensory afferent impulses from organs in the chest and abdomen through the vagus nerve, and it is also involved in the sensation of taste in the anterior tongue through the chorda tympani nerve. Anatomical medullary brain lesions have been thought to induce physiological autonomic abnormalities resulting in sudden death. The mechanism is unknown[8].

Pathological findings from a large number of cases taken together have led some investigators to suggest that sudden infant death syndrome may be a subset of sudden unexpected death related to medullary brain lesions[3,23-25]. This implies that biochemical medullary brain lesions may also induce physiological autonomic abnormalities resulting in sudden death, in as much as an abundance of sudden infant death syndrome research in recent years has focused on medullary neurotransmitter abnormalities, especially involving serotonin[26]. Similarly in adults, a recent neuropathology study[27] of sudden death in various subpopulations of multiple system atrophy found that depletion of medullary serotonergic neurons was associated with sudden death, the leading cause of death in multiple system atrophy. And while studying seizure disorders, a few investigators have speculated that sudden unexpected death in epilepsy may also be a subset of sudden unexpected death related to medullary brain lesions[2] based in part on the autonomic stigmata of associated seizure activity, including central apnea and laryngospasm[8,17,28].

CHEST PAIN FROM THE BRAIN

Sudden death probably occurs infrequently compared to the many non-fatal manifestations of abnormally functioning autonomic nuclei related to small medullary brain lesions. Non-fatal events may be experienced by patients as

symptoms in the chest, abdomen[7], and elsewhere; yet in these instances the primary illness is located in the medulla and not in the organ where symptoms are experienced. Symptoms may include nausea and vomiting[29], pain in the chest or epigastrium[7], and shortness of breath[13,15]. An occasional manifestation is Ondine's curse, a syndrome of sleep apnea with preserved wakeful voluntary control of respiration occurring after some medullary infarctions[16] and in association with other types of medullary lesions[12], including medullary plaques in multiple sclerosis patients who subsequently died during their sleep[9]. Most patients with medullary brain lesions will likely not experience sudden death, but the risk of sudden unexpected death in patients with medullary brain lesions is unknown.

ISCHEMIC AUTONOMIC UMBRA

The findings of case reports suggest that in some medullary autonomic nuclei, focal areas of parenchymal tissue, often dendritic, may become ischemic when excessive neuronal stimulation results in transiently elevated metabolic requirements exceeding levels that can be supported by the perfusion generated from maximum vascular flow in a fixed watershed area. Such focal medullary ischemia and infarction are often not related to vascular occlusion, or to vascular disease in general, as much as to a mis-match of accentuated metabolic activity and vascular flow which is insufficient in this somewhat unusual physiological setting. Small vessel disease, however, related to diabetes or hypertension may be a contributor. As evidence of watershed vascular insufficiency, investigators have reported small infarctions in watershed areas of the solitary tract nucleus[10,19].

Such pathological findings suggest that increased metabolic requirements and the formation of medullary ischemic lesions may be induced by repetitive neuronal stimuli originating in autonomic sites outside of the medulla, such as during intermittent episodes of heart failure[10,19]. Some focal dendritic sites on medullary autonomic nuclei capable of receiving visceral sensory stimulation *via* afferent neural pathways may experience the formation of ischemic lesions when this stimulation becomes persistent and repetitive. At the convergence of a limited vascular capacity and accentuated metabolic requirements is the spatial distribution that might be called an "ischemic autonomic umbra", the converse of an ischemic penumbra. Chronic and severe neuronal bombardment from outside the medulla may in some instances result in the formation of a small anatomical ischemic lesion or infarction, which may then itself trigger a significant systemic physiological event involving thoracic organs, possibly fatal, or possibly not[10,19].

PATIENT CARE

In today's world many patients with medullary autonomic lesions would never receive a neurological evaluation because their symptoms would not seem appropriate for referral to a neurologist. Additionally, the clinical recognition of medullary autonomic lesions often does not fit the traditional clinical neurology construct of identifying deficits in motor function, sensory function, or cognition, all of which may remain essentially normal in these patients. And medullary brain imaging is often not helpful due to bony artifacts and inadequate resolution capability.

In the year 2050 patients with chest and abdominal complaints will probably undergo evaluation specific to those areas, just as they would today. But if testing is negative, some will likely be considered candidates for medullary brain evaluation. Initial diagnostic testing of the patient possibly by magnetic resonance imaging, positron emission tomography, ultrasound, nuclear medicine, and/or other modalities available at that time will establish a profile of initial conditions within the brain medulla regarding lesions, general tissue architecture, and regional blood flow patterns. A computerized 3-dimensional reconstruction of this information will prepare the patient for treatment, which may include brain dentistry, following any acute management that might be necessary. Essential to the development of medullary neurology will be advances in non-invasive radiology that will yield 3-dimensional dynamic imaging of both medullary parenchymal tissue and medullary vasculature in significant detail, exceeding the resolution capability that is available today.

BRAIN DENTISTRY

In the context of medullary neurology, computer-assisted dental applications may become important for two reasons. First, some of the sensory input that terminates in medullary nuclei begins in the peri-dental and peri-oral anatomy, just as some peri-oral motor activity emanates from medullary motor nuclei. And second, the relative proximity of the mouth to the brain together with its accessibility makes the mouth a location in which to install implantable appliances that might potentially be used to enhance medullary blood flow, stabilize electrical activity in the medulla, and perform other functions as well. Brain dentistry, as described here, is a branch of medical science concerned with using dental applications in the treatment and monitoring of brain disorders.

ELECTRICAL STIMULATION

As a precursor of brain dentistry, the use of electrical stimulation in the management of neurological illness is still in its infancy but has attained several important milestones. Brain dentistry will likely begin by utilizing electrical stimulation of cranial nerves and building on the experience gained from the use of vagus nerve stimulation. Vagus nerve stimulation has been successfully used in the treatment of epilepsy; and in epilepsy patients it has also been shown to increase blood flow in the medulla as well as in other areas of the brain[30]. Many sensory autonomic afferent fibers of the vagus nerve begin in the chest and abdomen and terminate in the solitary tract nucleus in the medulla. Vagus nerve stimulation follows those fibers to

this critical area, and then apparently goes on to stabilize electrical activity throughout the cerebral cortex to prevent seizure activity by a mechanism yet unknown.

Corroborating this is an animal study in which the solitary tract nucleus was electrically stimulated directly, resulting in increased cerebral blood flow as well as enhanced synchronization of the electroencephalogram[31]. And another animal study showed that vagus nerve stimulation significantly reduces the size of induced brain infarction by an unknown mechanism which is nonetheless independent of increased cerebral blood flow[32], thereby implying an additional mechanism of neural protection. In light of these findings it may not be surprising that direct electrical stimulation of the cerebral cortex[33] in animals protects that cortex from induced ischemia by mechanisms that are antiapoptotic, angiogenic, and anti-inflammatory. But more important to brain dentistry may be the indirect stimulation of a specific area of brain tissue by functionally stimulating peripheral nerves that lead to that specific area; and animal studies have shown this to significantly reduce the size of induced infarctions[34].

MOLAR MODULE

By the year 2050 "molar modules" may be among the most widely used dental appliances for brain dentistry in adults, due in part to the relatively large size of molars, as well as their posterior position in the mouth. An implanted molar module might consist of a permanent intraosseous metallic hardware casing which could hold computer chips and/or software that could be removed, updated, and replaced *via* a removable extraosseous dental crown. The site of implantation on the alveolar ridge would maintain the integrity of the dental arch and be consistent with overall dental health and dental occlusion. The molar module might fill a space previously made available by the extraction of teeth. Although there has been no previous experience using molar modules or brain dentistry in either animal models or humans, their usefulness is very plausible.

CHORDA TYMPANI NERVE

Brain dentistry may utilize computerized electronic stimulation of the chorda tympani nerve *via* a submucosal wire from the molar module to a site where the chorda tympani nerve runs together with the lingual nerve. This is a site frequently used by dentists for the blind injection of local anesthetic agents to anesthetize one side of the tongue together with the adjacent gingiva when performing procedures on the mandibular teeth. The chorda tympani nerve mediates taste sensation from the anterior 2/3 of the tongue, and is largely an innocent bystander for purposes of the dental injection.

Stimulation of the chorda tympani nerve indirectly stimulates the rostral third of the solitary tract nucleus of the medulla *via* functional connections, just as vagus nerve stimulation indirectly stimulates the caudal 2/3 of the solitary tract nucleus. Stimulation of the chorda tympani nerve would also indirectly stimulate the superior salivatory nucleus of the medulla *via* fibers which innervate the submandibular and sublingual glands in the floor of the mouth. Both vagus nerve stimulation and chorda tympani nerve stimulation may ultimately be utilized as treatment modalities in medullary neurology.

The development of wireless communication between the molar module and a secondary transmitter placed at the nerve site would minimize the invasiveness of the procedure to place a secondary transmitter and might open the possibility of blind transmucosal or percutaneous injection of a very small secondary transmitter, inasmuch as a wire connecting it to the molar module would be unnecessary.

Molar modules might eventually be multifunctional with roles in both monitoring and therapy. Cardiac rhythm and local tissue chemistries might be recorded and transmitted to a remote data base or mobile device. Synchronized stimulation of the auditory nerve by sub-audible sound pulses would indirectly stimulate the cochlear nucleus in the medulla. Future research will determine the value of these potential therapeutic modalities and others[35-37]. Some of the potential general goals of brain dentistry are to provide neural protection to vital centers of cardiac and respiratory function and to enhance their performance by optimizing blood flow, preventing ischemic injury, and enhancing electrical stability.

RECENT RELEVANT RESEARCH

Firstly, there have been no research publications regarding brain dentistry specifically - but medical investigators have recently been studying ways to prevent sudden deaths in vulnerable patient groups that have relevance to events in the medullary autonomic nuclei. The results of an international trial studying prevention of sudden death and near-death cardiac events in 1325 patients who had heart failure with central sleep apnea[38] have recently been reported. In this trial the patients were given a treatment which augmented pulmonary ventilation nocturnally and presumably improved systemic blood gasses nocturnally. The study, however, ignored the issues of neuro-electrical instability in the medullary autonomic nuclei, and it ultimately concluded that the ventilatory assistance given to the patients did not improve their outcomes, but in fact worsened them[38].

An alternative therapy under investigation is phrenic nerve stimulation. A recent international trial of only 57 patients with central sleep apnea who received unilateral phrenic nerve stimulation[39] showed that it was both safe and effective, even for those who also had heart failure. Although primarily a motor nerve (to the diaphragm), the phrenic nerve carries both sensory and autonomic fibers as well. Phrenic nerve stimulation may possibly have a modulating effect on medullary autonomic nuclei, which might help to prevent adverse cardiac events and improve patient outcomes.

Lastly, to the extent that vagus nerve stimulation is a

proposed preventive therapy for sudden unexpected death related to medullary brain lesions, it might be expected to reduce or eliminate the incidence of sudden unexpected death in epilepsy in the intractable epilepsy patients who receive it as treatment. But a recently published study[40] of 466 patients showed that vagus nerve stimulation did not influence the incidence of sudden unexpected death, although its data were collected between 1995 and 2010 and reflected the technology and methods of that time-frame[40]. Other investigators[41] of vagus nerve stimulation in epilepsy patients, however, have reported a favorable cardiac electrical stabilization, which encourages further research. And only very limited research has been done regarding the specific electronic parameters for stimulation of either the vagus or phrenic nerves, and this could greatly influence outcomes. Much more research is needed.

CONCLUSION

Vagus nerve stimulation has been used with relative safety and effectiveness to treat epilepsy, whereby it is thought to stabilize electrical activity in the brain and has been shown to increase blood flow in the medulla. Vagus nerve stimulation indirectly stimulates the solitary tract nucleus, an autonomic site most often involved in cases of sudden unexpected death related to medullary brain lesions, and where blood flow and electrical stability have been called into question.

It is plausible that vagus nerve stimulation might be used in the prevention of sudden unexpected death related to medullary brain lesions as well as non-fatal symptoms, such as "chest pain from the brain", possibly caused by ischemia and electrical instability in medullary autonomic nuclei. In future years, electrical stimulation of the chorda tympani nerve may be used to indirectly stimulate the solitary tract nucleus with the same goals.

A vast frontier within a small space, the medulla oblongata will likely be the focus of some of the most significant medical advances of the 21st century. Brain dentistry will probably play an important role in both monitoring and therapy related to the brain in general as it accompanies the development of medullary neurology.

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REVIEW

Time windows for postnatal changes in morphology and membrane excitability of genioglossal and oculomotor motoneurons

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Abstract

Time windows for postnatal changes in morphology and membrane excitability of genioglossal (GG) and oculomotor (OCM) motoneurons (MNs) are yet to be fully described. Analysis of data on brain slices *in vitro* of the 2 populations of MNs point to a well-defined developmental program that progresses with common age-related changes characterized by: (1) increase of dendritic surface along with length and reshaping of dendritic tree complexity; (2) disappearance of gap junctions early in development; (3) decrease of membrane passive properties, such as input resistance and time constant, together with an increase in the number of cells displaying sag, and modifications in rheobase; (4) action potential shortening and afterhyperpolarization; and (5) an increase in gain and maximum firing frequency. These modifications take place at different time windows for each motoneuronal population. In GG MNs, active membrane properties change mainly during the first postnatal week, passive membrane properties in the second week, and dendritic increasing length and size in the third week of development. In OCM MNs, changes in passive membrane properties and growth of dendritic size take place during the first postnatal week, while active membrane properties and rheobase change during the second and third weeks of development. The sequential order of changes is inverted between active and passive membrane properties, and growth in size does not temporally coincide for both motoneuron populations. These findings are discussed on the basis of environmental cues related to maturation of the respiratory and OCM systems.

Key words: Development; Motoneurons; Respiratory system; Oculomotor system; Neuronal plasticity

Core tip: For more than 2 decades, numerous studies have tried to describe time windows of changes of membrane properties of motoneurons. This review aims to show what mechanisms are implied in those changes as well as how they are triggered. Our findings are focused on genioglossal and oculomotor motoneurons from birth to adult age. The perspective adopted is the description of how those changes correlate with both intrinsic and extrinsic factors. Data in this review is relevant to understand pathologies related to development.

Carrascal L, Nieto-González J, Pardillo-Díaz R, Pásaro R, Barrionuevo G, Torres B, Cameron WE, Núñez-Abades P. Time windows for postnatal changes in morphology and membrane excitability of genioglossal and oculomotor motoneurons. *World J Neurol* 2015; 5(4): 113-131 Available from: URL: http://www.wjgnet.com/2218-6212/full/v5/i4/113.htm DOI: http://dx.doi.org/10.5316/wjn.v5.i4.113

INTRODUCTION

For the past 20 years, our lab has carried out research in order to understand how the anatomical and electrophysiological properties of MNs may change during postnatal development. Our studies have included analyses of rat MNs during their first month of life, from birth to day 30, when they become young adults. Our work has focused on respiratory MNs of the hypoglossal nucleus (genioglossal subpopulation, GG)[1-8], as well as of the oculomotor (OCM) nucleus[9-13]. The genioglossus is innervated by the ventromedial section of the hypoglossal nucleus[14]. The genioglossus is responsible for tongue protrusion and is activated before the diaphragm during respiration in order to keep the upper airway open[15]. MNs within the OCM nucleus innervate extra-ocular muscles[16] and drive eye movements[17-19]. Our studies have incorporated *in vitro* techniques with brain slices that can keep the tissue alive for hours. In these slices, it is possible to perform intracellular recording techniques and simultaneous labeling that allow for the morphological analysis of the cells recorded[1,3,5,7,9-11,13,20]. In this *in vitro* preparation the ionic setting can be easily controlled while the neurotransmitters and the drugs are being added to the extracellular medium[2,6,12,21-24]. Our results reveal that both pools of MNs undergo important modifications in their morphological and physiological characteristics during postnatal development. These changes are likely to start in embryologic stages and that what we are showing is the achievement of the typical characteristics of the adult phenotype[25-27].

For the purpose of comparison, data from GG and OCM MNs were grouped in P1-P5, P6-P10, P11-P15, and P21-P30[1-13]. A detailed comparison of the results obtained could provide information on: (1) the existence of a common maturation sequence in mammalian MNs; (2) the description of the progression of the physiological and anatomical features to reach an adult stage; (3) the different strategies and time windows that are used in the sequence of maturation; and (4) the causes behind all these phenomena. The identification of the time windows in which changes of morphological and electrophysiological properties take place would make these MNs a suitable model in order to study the mechanisms and molecules that are involved in such changes. To understand the existence of time windows of changes, we must keep in mind that the adult neuronal phenotype is shaped by a combination of genetic and epigenetic features[28]. Therefore, some of the changes that we present could also be a consequence of internal watches[29], or changes in trophic factors and/or synaptic inputs converging on MNs with age, or probably due to modifications that affect the properties of target muscle fiber composition[30-33].

DENDRITIC TREES MODIFY THEIR COMPLEXITY DURING POSTNATAL DEVELOPMENT

Dendrite morphogenesis involves an active and complex process of formation, maintenance or elimination of dendritic branches[34-37]. We have observed that the number of primary dendrites per MN is approximately 6, for the GG MNs, and 5 in the case of OCM MNs, numbers that remain unchanged with age[5,11]. However, the tree is largely remodeled during development. Dendritic trees of GG MNs are equally complex at birth and in the adult age, but they go through a stage of transient simplification (reduced complexity around P15)[5] during development. The dendritic complexity observed at birth gradually decreases during the first ten days in the number of branches per neuron, branch order, and number of terminal branches per neuron (Figure 1A-C). The elimination of dendritic branches (with a complete loss of the 6th-8th order branches) tends to increase the symmetry of the tree (schematically represented in Figure 2C). Then dendrites recover at P21-30 in the adult, exhibiting a similar complexity level as the one found in the newborn. This pattern of postnatal maturation in dendritic complexity was also described for spinal MNs[38,39]. However, a postnatal simplification of the dendritic tree may not be a general principle governing postnatal maturation of MNs, as proposed by Nuñez-Abades *et al*[5]. A different temporal pattern of dendritic complexity was later found in OCM MNs (Figure 1A-C). During the first stage (up to P10), the number of first order dendrites did not change, but the number of branches constantly increased as being observed in the number of branches per neuron, the branch order and the number of terminals per neuron (Figure 1A-C). During the second stage, the number of

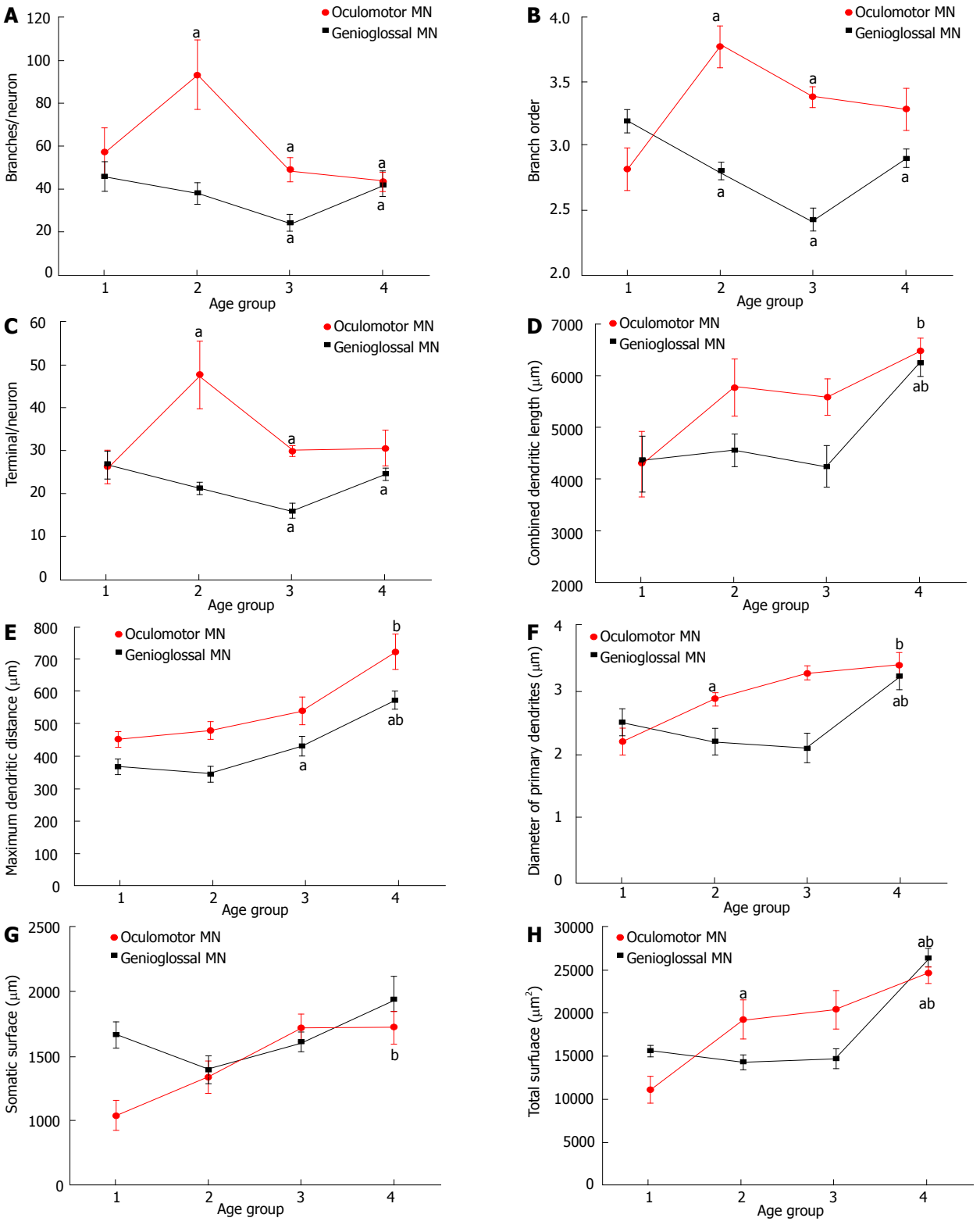

Figure 1 Postnatal maturation of morphological properties of motoneurons from genioglossal and oculomotor nuclei. A-C: Changes in dendritic complexity measured as number of branches per neuron (A), branch order (B) and number of terminals per neuron (C). Note that in GG MNs complexity decreases up to P15 and then increases, while in OCM MNs there is an increase up to P10 and then decreases. The 2 opposite development strategies lead to the same outcome in the adult rat when compared with initial values; D and E: Changes in neuronal length measured as combined dendritic length (D) and maximum distance from soma to dendritic terminal (E). Note in D-E that dendritic length progressively increases for both populations of MNs with the most relevant changes at the late stages of development; F and H: Changes in neuronal size measured as diameter of primary dendrites (F), somatic surface (G) and total surface area (H). Note that in F and H OCM MNs grow between P1 and P10, while GG MNs increase mainly between P15 and P30. OCM MNs show a slow growth of the somatic surface along development, while it is already established at birth in the case of GG MNs. In this figure and the following: (1) the plots illustrate mean values for each parameter and age for OCM (red circle) and GG (black square) MNs; (2) measures are expressed in mean ± standard error; (3) the "a" indicates statistical significance between two consecutive age groups; and (4) the "b" represents statistical significance between age group 1 and age group 4. The age groups 1, 2, 3 and 4 correspond to P1-P5, P6-P10, P11-P15 and P21-P30, respectively. The data from GG[5,7] and OCM[11] come from previous studies. MNs: Motoneurons; GG: Genioglossal; OCM: Oculomotor.

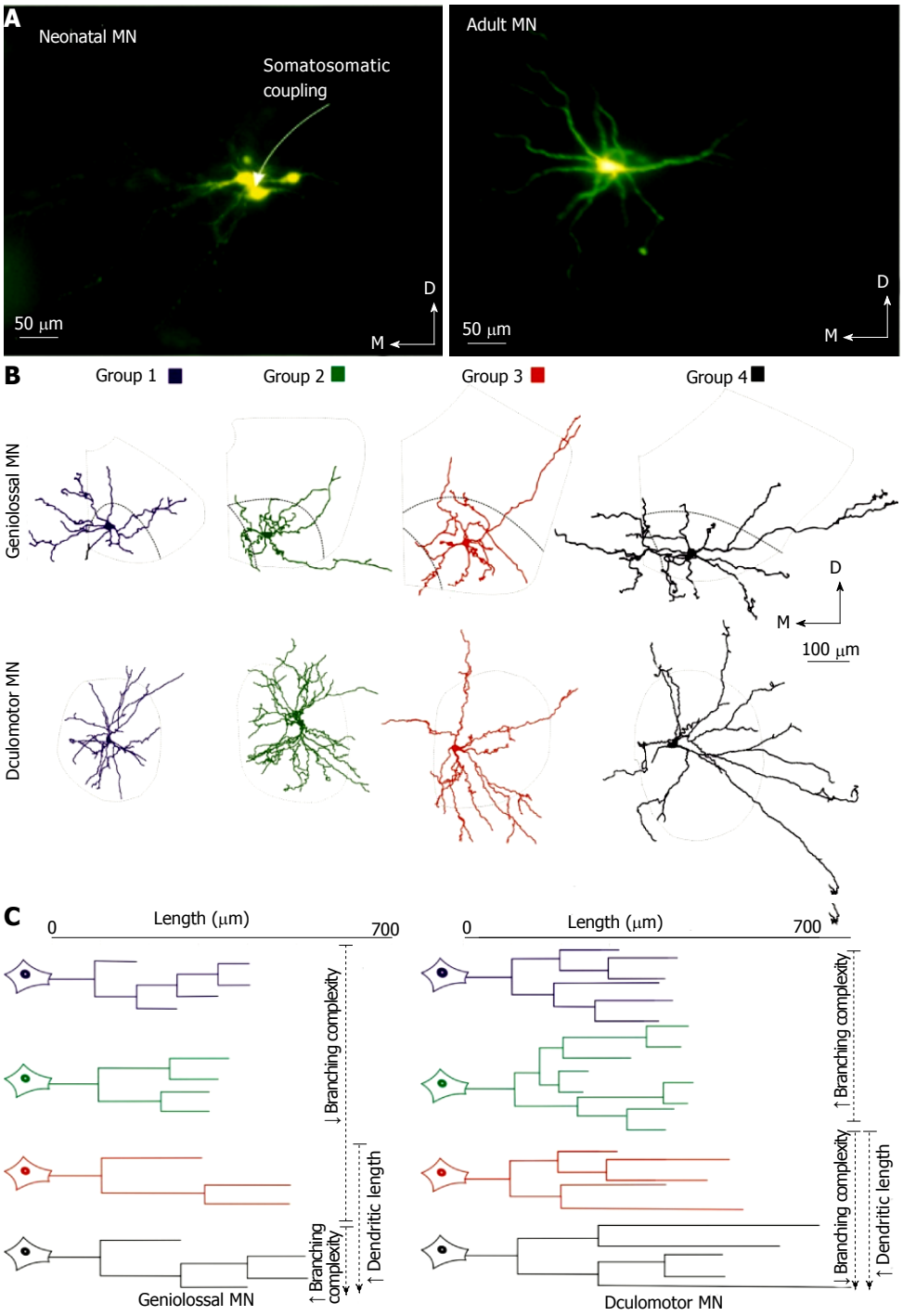

Figure 2 Summary of the main morphological changes of motoneurons from genioglossal and oculomotor nuclei. A: Photomicrographs of representative GG MNs injected intracellularly with Lucifer yellow in a newborn (left image) and juvenile adult rat (right image). Note the presence of coupling between neonatal MNs. Only one cell was injected, however 3-4 are labeled; B: Changes in nucleus size and dendritic arborization orientation of MNs during postnatal development. It is remarkable that dendrites in the younger MNs are restricted to the nucleus boundaires, whereas the 2 oldest groups show some portions of dendrites outside those limits, preferably in the ventrolateral axis. The outer line indicates the boundary of the nuclei, and the inner line shows the limits of the GG nucleus; C: Dendrograms for a representative dendrite for each age group of GG (left) and OCM (right) MNs. Note the growth in length for both groups of MNs and the changes in dendrite architecture that take place during development. The data from GG[3,5] and OCM[11] come from previous studies. MNs: Motoneurons; GG: Genioglossal; OCM: Oculomotor.

branches went down to newborn values[11]. The results described above may indicate that there is not a single maturational pattern of dendritic complexity in MNs. However, the observed changes in dendritic complexity may underlie a strategy that allows for dendritic elongation, as reported by Cameron *et al*[38].

DENDRITES ELONGATE DURING POSTNATAL DEVELOPMENT

The enlargement of dendrites during postnatal development is a common characteristic for every pool of MNs studied, including brainstem and spinal MNs of

different species[5,11,38-42]. In GG MNs, dendritic combined length is maintained from birth to day 15 (Figure 1D) and they show an evident tendency to increase in maximum dendritic length (Figure 1E). Later, between P15 and P21-30, this proliferation of branches, that occurs in the intermediate parts of terminal branches[5], significantly augment the combination of dendritic length and maximal distance (Figure 1D and E). In accordance with that data, sholl diagrams evidence how adult MNs exhibit dendrites about two-fold larger than those stated around P10 in OCM nucleus MN[11]. In OCM MNs, therefore, dendritic elongation takes place between P10 and P21-30, in maximal dendritic distance (Figures 1E and 2C), and gradually from birth to P21-30 in dendritic combined length (Figures 1F and 2C). An interesting aspect is to know whether neurons elongate in preferential directions to establish the adult territories.

The lengthening of neonatal mouse lumbar MNs during the first 2 week after birth can be compared with the growth of the spinal cord[40]. However, the remarkable growth in length of GG and OCM dendrites is bigger than the size the nuclei increase. Then, dendrites can be found outside the boundaries of the GG and OCM nuclei in adult MNs in a area larger and in a higher percentage than those for newborn MNs (Figure 2B). Studies carried out on adult rat hypoglossal MNs[43] indicate the existence of extranuclear dendrites that are distributed along four separate areas, including the nucleus of tractus solitaries, the nucleus raphe obscurus, the medullary reticular formation, and the contralateral hypoglossal nucleus. We have found that these dendritic domains are not established at birth but rather their proliferation shows up during development[5]. Two and three-dimensional analyses showed a new tree configuration for GG MNs from birth up to days 5-6 consisting of the resorption of dendrites in the medial, dorsal, and dorsomedial directions (Figure 2B). Dendrite growth expands in all directions between days 13-15 and 19-30, but with a greater increase in the medial and lateral sectors (Figure 2B), and dendrites are now placed outside the nucleus, mostly oriented towards the dorsolateral and ventrolateral regions, particularly in the adult age. As described for the GG nucleus, dendrites of OCM MNs of adult rats extend outside the nucleus in a larger area and in a higher percentage than those found in newborn MNs (Figure 2B). Dendrites in the transverse section for P11-P15 and adult MNs, are mainly oriented outside the nucleus in the dorsal and ventrolateral directions.

An interesting question that arises is how dendritic fields and the boundaries of dendritic fields are established[36,44]. We must bear in mind that dendrites of the GG and OCM MNs remain inside the boundaries of their nuclei from birth to P10 (Figure 2B) with clear signs of dendritic retractions that keep them inside the nuclei displaying a round-shaped distribution. It is known that the repulsive dendro-dendritic contacts determine the basis of contact-mediated inhibition of dendritic growth[45]. Then, our findings might suggest that those dendro-dendritic interactions also constitute a regulation element for GG and OCM MNs in the first 10 d of life. Another question is how the direction of dendrite out-growth is determined. A large number of transcription factors regulate various aspects of dendrite development[36,46]. However, the way in which they regulate the size and the pattern of dendritic fields in order to produce the MN identity is not yet fully understood[47-51]. Furthermore, local signals activate processes of arborization and elongation of the growth cones that are located in the terminal branches of the dendritic trees[36,46,52,53]. Extrinsic signals, such as neurotrophins, and neuronal activity seem to induce dendrite development modifying the organization and dynamics of the cytoskeleton[36,54-57]. We have found that GG and OCM MNs show a differential enlargement of dendrites in some orientations from P10 to P21. Then, it can be proposed that dendrites in GG and OCM MNs respond unevenly to extracellular cues, suggesting that they are asymmetrically distributed in different dendrites. Furthermore, the observed dendritic growth in particular time windows may be related to the arrival of new synaptic inputs[35]. In GG MNs, dendrites that extend dorsolaterally into the tractus solitaries between P15-P30 may synaptically connect from peripheral respiratory receptors[58] that are important to induce hypoglossal reflexes (*i.e.*, swallowing)[59]. Dendrites extending laterally could be targeted by trigeminal afferents that are related with coordination of the tongue and jaw[60], and dendrites orientated ventrally could be the target of innervation from nucleus raphe obscurus, related to state-dependent activity (*e.g.*, sleep/wake, rest/exercise)[61] and mediating CO_2 chemosensitivity[62] or from excitatory and inhibitory respiratory premotor neurons[30,63-69]. The ventrally oriented dendrites in OCM MNs in P15-P30 would display a location closer to the medial longitudinal fasciculus. These vestibular afferents elicit eye movements at around P21[70-71]. In addition, the elongation and simplification of dentritic trees with postnatal development may underlie the stratification of different synaptic inputs[72]. and, in OCM MNs, they may provide a means for the separate control of visuomotor and vestibular functions[73].

POSTNATAL DENDRITIC RESHAPING GOES ALONG WITH GAP JUNCTION WITHDRAWAL

Gap junctions couple MNs at the embryonic and the early postnatal periods[25]. This coupling is present in newborn GG MNs up to 8 d after birth as demonstrated by intracellular injection with Lucyfer yellow (Figure 2A)[3]. A similar finding was found in OCM MNs[11]. The loss of electronic coupling in MNs with age is allows for the acquisition of individual motor units[74]. While present in early postnatal stages, gap junctions contribute to

synchronous firing[75] and, likewise they could help to synchronize collective discharge in GG MNs. This has the immediate effect of producing a strong and uniform tongue protusion that is required in important motor tasks (such as sucking, breathing, and swallowing) from the moment the animal is born[3]. However, it is not easy to extend this hypothesis to ocular MNs, since the latter are only ready in P21. This is the precise moment when eye movements are performed as a result of the visual and vestibular stimuli[70,71]. Another hypothesis is that this early coupling before P11 helps to establish the necessary "prewiring" for the progressive formation of neural circuits[76]. When gap junctions are removed the polyneuronal innervation of muscle fibers is also eliminated in a process that seems to be under the control of trophic factors[77,78]. In fact, the timing for that disappearance may be disrupted when the muscle is paralized in the neonatal rat, demonstrating that trophic factors arising from the target muscle are needed to maintain gap junctions in MNs[79]. Thus we propose that coupling in GG and OCM MNs is removed when polyneuronal innervation has also disappeared in the muscles that they innervate, and when prewiring of neuronal circuits on those MNs has been established.

POSTNATAL INCREASE IN SIZE IS NOT A CONTINUOUS PROCESS

Somatic and dendritic neuronal size is not established at birth[38]. In a pioneer study, researchers found that the growth in membrane surface area of developing spinal MNs of the cat can be considered a continuous process[80,81]. However, our investigations of phrenic MNs in the cat[38], as well as in GG MNs of the rat[7] disagree with that hypothesis. In fact, GG MNs (from birth to P15) were characterized by a lack of growth in dendritic diameter and dendritic surface area (Figure 1F-H). In this time window, maturation results in more surface area being placed at distances farther away from soma by the redistribution of the preexisting membrane (Figure 2C)[7]. Later, beyond day P15, the dendritic surface area doubles because of the generation of new terminal branches and the increase in dendritic diameter at all branch orders (especially significant was the increase in the 1st order diameter, see Figure 1F). Growth in diameter in cat spinal MNs has also been reported to occur late in development[38,39]. However, an earlier time window for growth in dendritic size was found in OCM MNs. In these MNs, dendrites increase exponentially until around P10 (Figure 1F-H)[11]. In this period, the membrane area of dendritic trees increases by a greater arborization. Later (beyond P10), maturation produces a greater area farther away from the soma, by the use of the pre-existing membrane, but at the expense of lowering the complexity of the dendritic arborization (Figure 2D). Despite growth observed in somal dimensions in OCM MNs measured postnatally (Figure 1G)[7,11], the dendritic to somal surface area ratio increases postnatally in GG and OCM MNs, as concluded for other similar studies on developing spinal MNs[38,39,81]. In general, it seems that there is more dendritic surface area available for afferent synapses in developing MNs than in newborn MNs.

A DECREASE IN TIME CONSTANT AND INPUT RESISTANCE CHARACTERIZES DEVELOPMENT

In Figure 3A we illustrate that the same current amplitude evokes a larger hyperpolarization in the youngest MN, which implies a larger input resistance when compared with the adult. Input resistance was about 50% less in GG motoneurons and about 25% less in OCM MNs (Figure 3B and C)[4]. This reduction is common to different pools of MNs[82-85]. Figure 3C depicts how the drop in resistance for GG MNs happens in a narrow time window between P10-P15, while the same drop takes place between P5-P10 in the case of OCM MNs.

As seen in Figure 3A, in newborn GG MNs (and also in OCM MNs, not shown), the voltage response to current negative pulses approaches a steady-state level exponentially. Furthermore, the relationship between current negative pulses and voltage response is almost linear (Figure 3B). As a response to negative current steps, adult GG MNs present a membrane potential rectification that is characterized by a depolarizing drift or "sag" (Figure 3A)[4]. This physiological phenomenon has also been reported in other motoneuronal pools[84,86-88]. The frequency of sag increases ten times gradually in GG and OCM MNs, without the appearance of a clear time window for changes[4,10]. An inward rectification current (Ih) is believed to be underlying this sag. This current is largely carried by sodium ions and can be blocked by extracellular cesium[2,89] and may participate in the postinhibitory rebound seen in the adult MN as illustrated in Figure 3A. The increasing frequency of sag with age is paralell to a bigger density of channels carrying Ih current (Figure 4)[90]. Although Ih current is half-active at rest, as demonstrated by voltage-clamp experiments[89,90], it is unlikely that this conductance underlie the decrease in input resistance during development[1,91].

If we accept that specific membrane capacitance stays unchanged during development, the decrease in time constant in MNs would be a consequence of the reduction in the specific membrane resistance[85]. In Figure 3D, we illustrate how the time constant in GG and OCM MNs falls around 40% and 30%, respectively, in the time window found for the decrease in input resistance. This coincidence in time framing points to one mechanism that can explain both phenomena: A decrease in specific membrane resistance. In summary, the decrease in time constant, input resistance, and probably specific membrane resistance must be genetically programmed during postnatal development for all MNs, and it is even observable in MNs in culture[29].

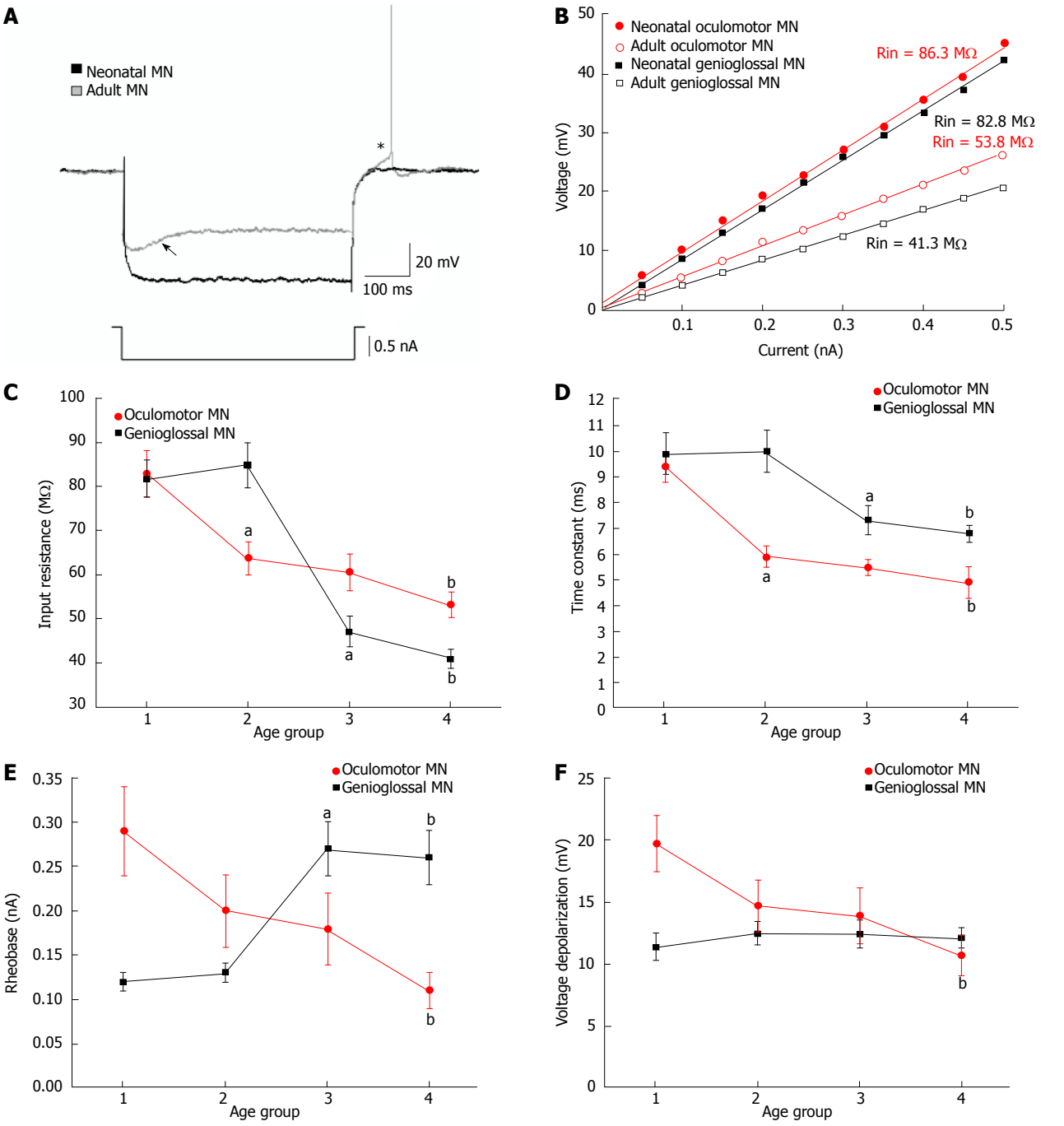

Figure 3 Postnatal maturation of passive membrane properties of motoneurons from genioglossal and oculomotor nuclei. A: Voltage membrane response for one representative GG neonatal MN and one representative adult MN to negative current pulses of 0.8 nA. As shown, the same current amplitude of current evokes a larger hyperpolarization in the youngest MN. Also note the presence of sag (see arrow) and postinhibitory rebound (asterisk) in the adult MN but not in the neonatal one; B: Relationship between current intensity and voltage response in neonatal and adult MNs: Neonatal OCM MN (filled red circle); adult OCM MN (open red circle); neonatal GG MN (filled black square); adult GG MN (open black square). The slope of the relationship determines input resistance. Note that, for both populations of MNs, input resistance decreases with development although this decrement is bigger for GG MNs; C-F: Plots illustrating changes on input resistance (C), time constant (D), rheobase (E) and voltage depolarization (F) during postnatal development for GG and OCM MNs. Input resistance and time constant decrease during development in both populations, while rheobase increases in GG MNs and decreases in OCM MNs. The "a" indicates statistical significance between two consecutive age groups; and the "b" represents statistical significance between age group 1 and age group 4. The age groups 1,2,3 and 4 correspond to P1-P5, P6-P10, P11-P15 and P21-P30, respectively. The data from GG[4] and OCM[10] come from previous studies. MNs: Motoneurons; GG: Genioglossal; OCM: Oculomotor.

However, the differential time window of changes in passive membrane properties for each population of MNs would lead to the conclusion that extrinsic factors trigger the onset of the change, revealing that each population might be specialized depending on their function.

The drop in specific membrane resistance within postnatal development could be attributed to a larger membrane surface[92]. Our data demonstrate a significant correlation between total membrane surface and input resistance in newborn and in adult OCM MNs[13]. However, when we combine neonatal and adult MNs

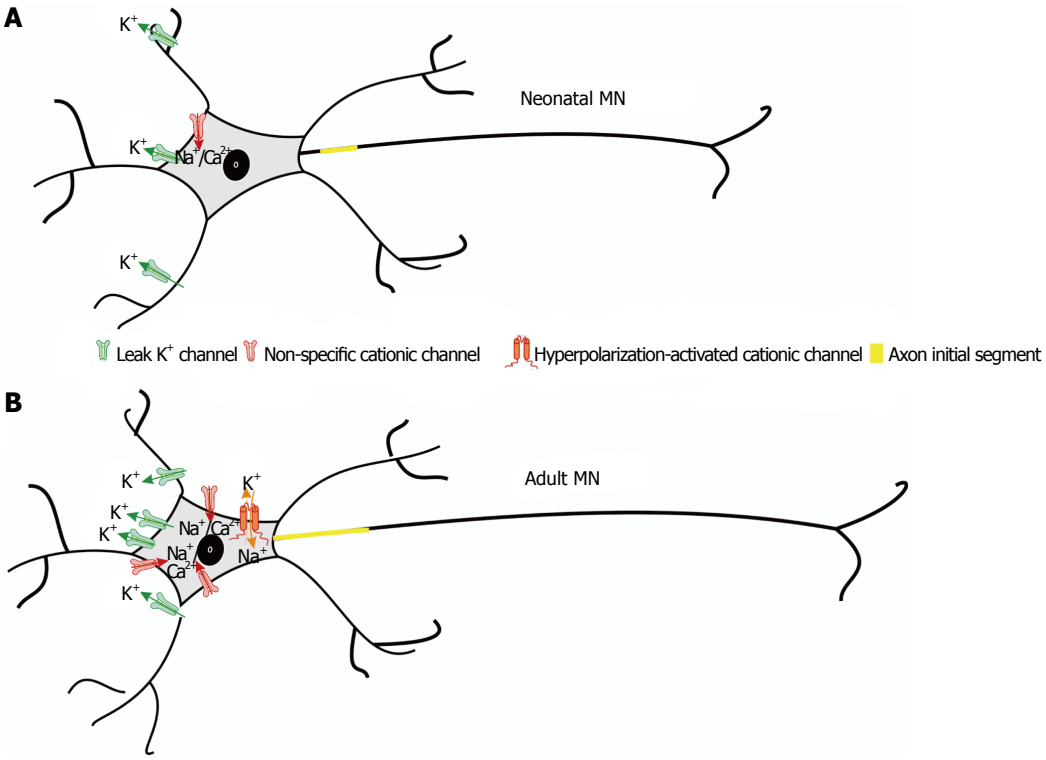

Figure 4 Hypothesis of mechanisms underlying input resistance and rheobase modifications during development. Schematic drawings illustrating proposed differences in ion channels (number, type and distribution) and axon initial segment (length and proximity to soma), between neonatal (A) and adult (B) MNs. Note that, in the adult MN, the axon initial segment is represented larger and closer to soma. Besides, in the neonatal MN, leak potassium channels are located more distal to the soma and in a less number. Hyperpolarization-activated cationic channels responsible to the sag are only present in the adult MN, with a high number of non-specific cationic channels responsible for the persistent calcium and sodium currents. MNs: Motoneurons.

in a single group, size and input resistance do not correlate well[8,13]. This disagreement could be explained by the fact that changes in input resistance and size are not linked, as demonstrated in spinal MNs[93].

The proliferation of tonically active synaptic inputs was used to analyze the postnatal decrease in the passive membrane properties in rat GG MNs. Both hypoglossal and OCM MNs may be receiving GABA, glycine, and glutamatergic synaptic inputs that may be tonically active[23,24,94,95]. Then, developmental alterations in the number or kinetics of the neurotransmitter receptors may produce some of the electrophysiological observable changes[6,95-97]. The role of the synaptic input was evaluated by the selective blockage of neurotransmitter release associated with action potentials, calcium-dependent and calcium-independent release in developing GG MNs[6]. From these experiments we concluded that: (1) synaptic input contributes to the resting conductance of the MN membrane under development; (2) the role that glycine/GABAA receptors may play to determine resistance becomes dominant in the adult, suggesting a proliferation of inhibitory synaptic inputs with age; and (3) the proliferation of synaptic inputs is not enough to explain the large decrease in input resistance occurring between days P10 and P15 in developing GG MNs. In OCM MNs, it seems that GABA, but not glutamate, may contribute to membrane resistance in juvenile rats[23,24]. On the other hand, noradrenergic and serotoninergic modulation in hypoglossal MNs has also been associated with significant changes in neuronal input resistance[97,98].

Second, we have studied whether a possible proliferation of K^+ channels during postnatal development could be the reason for the decrease in input resistance in GG MNs between P10-P15[2]. The addition of a potassium channel blocker, tetraethylammonium, to the extracellular medium in the presence of high magnesium largely increases both input resistance and time constant, indicating a major role for K^+ channels that are not related to synaptic transmission. More drastic changes occur when external barium is applied, known to be able to block the "leak" K^+ channel[99]. An additional manipulation of K^+ channels was obtained by the intracellular injection of cesium[2]. Thus, from these experiments it was concluded that cells with a low resistance have a greater number of cesium- and barium-sensitive channels than cells with a high resistance. Then, the current hypothesis (Figure 4) suggests that the main factor to explain the fall in passive membrane properties is probably an increase in the expression of a leak K^+ current over development, that is partly mediated by TASK-1 and TASK-1/3 heteromeric channels[100,101], between P10-P15 in GG that can be extended to OCM MNs[102]. Furthermore, both anatomical evidence[101] and the data obtained with a model for sympathetic neurons[103] applied to GG MNs[1] support a differential distribution of leak K^+ channels in dendrites. We

propose that the potassium conductances more distally located at birth are probably uniformly redistributed across the adult MN membrane (Figure 4)[1,2].

CHANGES IN SPECIFIC MEMBRANE RESISTANCE WOULD LEAD TO PHYSIOLOGICAL ALTERATIONS IN MOTONEURON EXCITABILITY DURING POSTNATAL DEVELOPMENT

The minimum injected current required to elicit an action potential (rheobase) is a measure of cell excitability[4,9]. Considering that the amount of depolarization required to reach threshold in GG MNs does not change with age (Figure 3F), the 2 times increase found in rheobase during postnatal development in these MNs must be the result of a decrease in specific resistance (Figure 3E). Supporting this conclusion is the fact that the increase in rheobase happens in a time window identical to the one shown by the decrease of the input resistance. This finding suggests that the membrane of the GG MNs behave as an ohmic membrane. By contrast, in OCM MNs, we found a gradual decrease in the rheobase with age (Figure 3E)[10] as found in cortical pyramidal cells with age[104]. These results may suggest that the postnatal development in rheobase depends on the population of MNs. In OCM MNs, the decrease in the rheobase (Figure 3E) goes along a decrease in the depolarization voltage needed to reach threshold (Figure 3F). Thus, in these MNs, the excitability within the nucleus increases in spite of the lower membrane resistance[9]. The drop of the voltage threshold with age in OCM nucleus MNs could motivated by an increase in long lasting Ca^{2+} currents and persistent Na^{+} conductance. These inward currents, which are activated at the subthreshold level, may produce excitation and be implied in MN recruitment[105-109]. Several studies report about these conductances in brainstem and spinal MNs[84,88,110,111]. If these currents actually increase during postnatal maturation[112], thus influencing spike threshold, they might explain the decreased depolarization voltage in adult OCM nucleus MNs. We propose that these currents are increased gradually during postnatal maturation (Figure 4), but their influence on action potential generation differs between the two pools. Different explanations could be given to explain the diminution of voltage threshold at postnatal age in OCM MNs. For instance, new findings have shown plasticity in the axonal initial segment that influences cell excitability[113]. A possible hypothesis is how synaptic deprivation or chronic depolarization can modify the location and extent of this spike triggering zone[114-116]. The enlargement of the axon initial segment, which goes along bigger voltage-gated sodium currents, decreases both the current and voltage threshold to trigger action potential[116]. The same can be proposed in OCM MNs during development (Figure 4). Extended studies on the modifications in ionic currents (voltage gated sodium current, persistent inward current, *etc.*) and in the axon initial segment should provide further insight to interpret the physiological bases of changes in the rheobase and voltage threshold during development. We have demonstrated that an active membrane property, namely voltage threshold, not associated with cell size - input resistance, is the one that determines the recruitment order of MNs during postnatal development[13]. Furthermore, we have also reported that voltage threshold is modulated by acetylcholine in OCM MNs[21] and this modulation is enhanced with age[12].

CHANGES IN ACTION POTENTIAL PROPERTIES WITH AGE

GG and OCM MNs undergo several changes in their action potential properties, and the subsequent medium afterhyperpolarization (mAHP), during the first 3 wk of life (Figure 5A-D). The first week is characterized by a decrease in the duration of the action potential and the mAHP in developing GG MNs. Even though no change can be observed in the resting membrane potential or action potential height during development, the action potential is shortened as a result of more rapid depolarization and repolarization stages. Duration of the action potential and mAHP in OCM MNs also diminishes half in time between the newborn and the adult ages, but these changes take place gradually, and more slowly than in the GG MNs, between the first two weeks (duration of the action potential) and the three weeks (mAHP) of development. One possible mechanism for the changes observed in action potential width is the increase in channel density or alternatively a more synchronized opening of voltage-gated Na^{+} channels and delayed rectifier K^{+} channels underlying action potentials[117-121]. Both mechanisms are proposed in Figure 5E to explain postnatal alterations in action potentials with age. The increase in channel density[117] may also be a consequence of the previously described changes in the axon initial segment length[116] with development. Considering that firing rate mainly depends on mAHP duration[122,123], a comparison of the mAHP data between the two pools is appropriate since it would produce a higher discharge rate in the adult cells. In Figure 5E, we also propose that a decrement in voltage-activated Ca^{2+} conductance with age, underlying the action potential afterdepolarization, could also be responsible of the decay in mAHP duration with development. This stage is known to depend on a Ca^{2+}-dependent K^{+} current[88,124]. A similar interpretation may be proposed to understand the behavior of other brainstem and spinal MNs[83-85]. The shortening of the mAHP is more evident in OCM (approximately 100%) than in GG MNs (approximately 25%) (Figure 5D)[4,10] as a consequence of a longer time

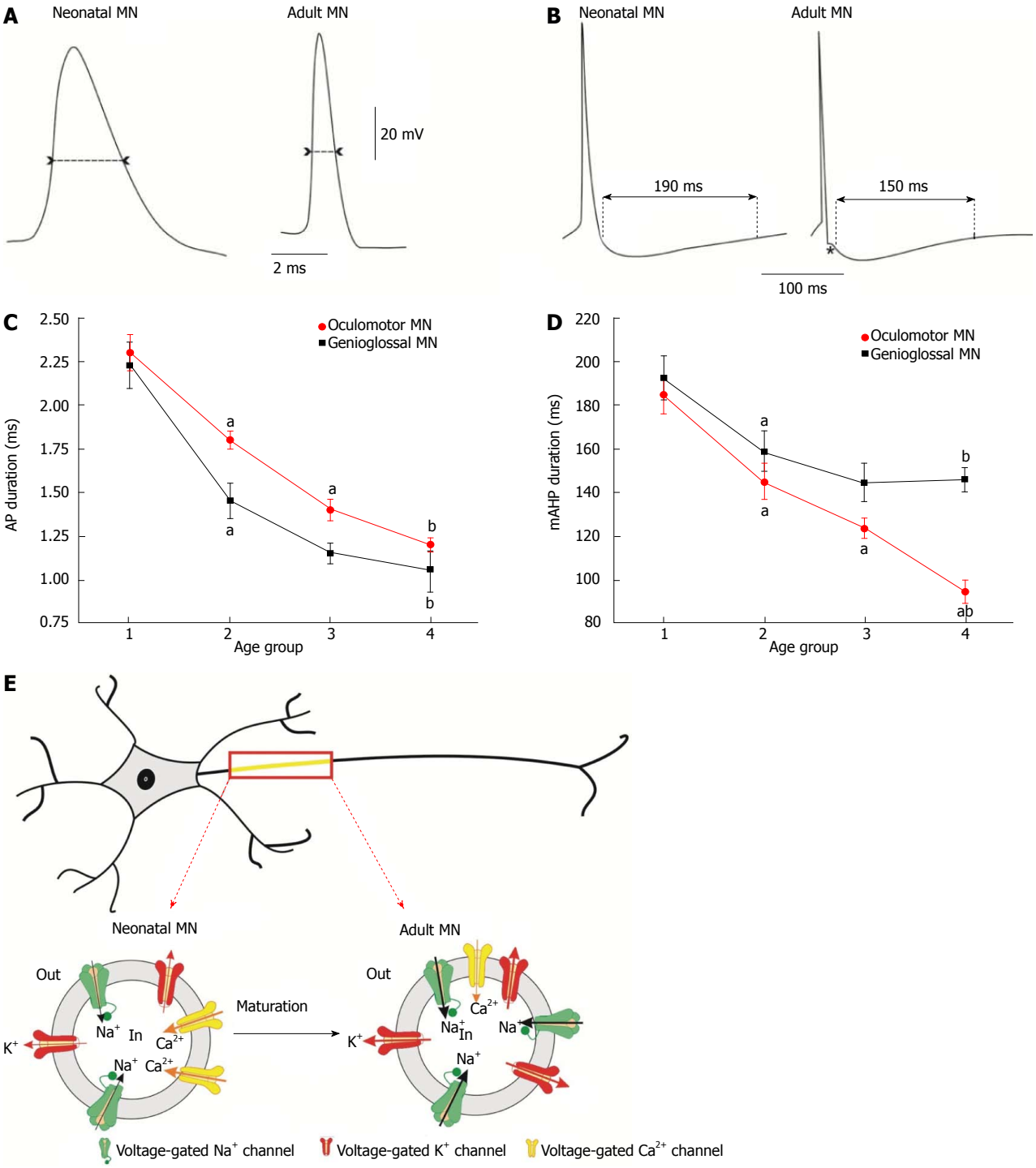

Figure 5 Postnatal maturation of action potential characteristics of motoneurons from genioglossal and oculomotor nuclei. A and B: Recordings illustrating a representative action potential from one neonatal and one adult MN, at two different time scales, emphasizing the duration of the action potential (A) and the duration of the medium afterhyperpolarization phase of the action potential (B). Note the shortening in both phases during development. Also remarkable the presence of afterdepolarization phase in the adult MN (see asterisk); C and D: Plots illustrating the changes on action potential duration (C), and medium afterhyperpolarization phase duration (D) during postnatal development for GG and OCM MNs. Both populations show a decrease in these parameters. However it should be noted that, in GG MNs, changes in the afterhyperpolarization phase cease to decrease at the second postnatal week and, in the OCM MNs, this decrease is bigger and continuous up to P30; E: Schematic drawing illustrating proposed differences in ion channels (number and kinetics) underlying action potentials between neonatal and adult MNs. Note, for the adult MN, a higher number of potassium and sodium voltage gated channels and larger conductances (thick arrows) when compared with the neonatal MN. We also proposed the existence of less voltage gated calcium channels with lower conductances (thin arrows) for the adult MNs. The "a" indicates statistical significance between two consecutive age groups; and the "b" represents statistical significance between age group 1 and age group 4. The age groups 1,2,3 and 4 correspond to P1-P5, P6-P10, P11-P15 and P21-P30, respectively. The data from GG[4] and OCM[10] come from previous studies. MNs: Motoneurons; GG: Genioglossal; OCM: Oculomotor.

window of changes (Figure 5D). Then, the decrement in voltage-activated Ca^{2+} conductance with age must be stronger in OCM MNs, since those conductances are lower in adult OCM than in hypoglossal MNs[125].

TIME-DEPENDENT CHANGES IN FIRING PROPERTIES: FIRING FREQUENCY, GAIN AND MAXIMUM FREQUENCY

At birth, all GG MNs display an adapting discharge pattern (Figure 6A). Later, after the first week, adapting firing pattern is converted to a non-adapting firing (phasic-tonic pattern, Figure 6A). It is possible that the progressive decrease in the duration of the mAHP found in these train discharges is the result of the progressive activation of a Ca^{2+}-mediated K^+ conductance[126] because processes of Ca^{2+} sequestration and extrusion[127] are not well developed in MNs at birth, allowing for an increase in the concentration of intracellular Ca^{2+} with each successive spike. By contrast, and regardless the age group, all OCM MNs repetitively discharge with a phasic-tonic pattern to sustained depolarizing currents. Therefore, the firing pattern is already established at birth in this population[10].

In Figure 6B, firing frequency gain was obtained from the slope of the F/I plot in four representative neurons (two of each MN pool). It is evident from the figure that gains are higher in adult than in newborn MNs in both nuclei (Figure 6C)[4,10]. GG MNs share with OCM MNs[4,10] and spinal MNs[83] a tendency to increase the firing rate with postnatal development. The main difference between the two populations is that the increase in gain extends to P15 in GG MNs but continues up to P30 in OCM MNs, resulting in a higher discharge rate in adult OCM MNs when compared with adult GG MNs (Figure 6C). The balance between tonic inward currents and the outward currents has been suggested to be a major determinant of the F-I relationship[27,91,125,128-131]. Physiological mechanisms that may underlie the trend toward higher discharge frequencies during postnatal development include an increase in the hyperpolarizing-activated mixed-cationic currents[90]; a rise in both persistent sodium conductance and long-lasting calcium current[88,107,109,111]; a decrease in the low-voltage-activated calcium currents[129]; and a reduction of A-type potassium current[84]. Neurotransmitter and trophic factors may be controlling most of these conductances and those underlying the mAHP[23,24,122,132-135].

Figure 6D illustrates changes of maximum frequency with age. Neonatal GG and OCM MNs have lower maximum firing frequency than the one found in the adult. Furthermore, increase in the maximum firing rate takes place between P16-P30 in OCM MNs, whereas in GG MNs the rise continues up to the adult stage[4]. An explanation for a higher frequency during development is a more rapid activation of the delay rectifier or a shorter inactivation stage of the voltage-gated Na^+ channels[136]. Furthermore, the maximum frequency of adult OCM MNs overcomes that of the newborn three times, while the increase in GG discharge is less than twice (Figure 3B). Then, we suggest that extraocular MNs develop a higher pattern of discharge to achieve their function of producing faster contraction times of the extraocular muscles when compared with the genioglossus and other skeletal muscles[137,138].

TIME WINDOWS OF CHANGES IN MEMBRANE PROPERTIES

A time window exists when a brain circuit that subserves a given function is specifically receptive to acquiring certain kinds of information, or when the circuit needs a signal for their normal development[28]. Changes in morphological and electrophysiological properties of the membrane can, for simplification purposes, be distributed in 3 distinct time windows, *i.e.*, the first, second and third-fourth weeks of life (Figure 7). We first describe changes in GG MNs (left of the Figure 7) and then changes in OCM MNs (right of the Figure 7).

In GG MNs the dendritic tree is simplified and gap junctions disappear during the first postnatal week, while the membrane surface is maintained. The action potential and the hyperpolarization stage diminish. The firing pattern becomes phasic-tonic. During the second week, the dendritic tree completes its simplification by augmenting its dendritic length. Also, membrane resistance and time constant decrease and there exists a compensatory change in the rheobase. During the third postnatal week, the dendritic complexity increases until reaching values found at birth. This increase was produced by the formation of new dendritic branches, as a consequence of the enlarging diameter of primary dendrites and the total dendritic surface. This dendritic re-organization was elaborated, in an asymmetrical way, on some axes mainly (*i.e.*, the ventrolateral axis) and it produces an increase of the dendritic length. During this third week, firing frequency gain and maximum frequency reach a significant increase that had slowly started at birth.

For the OCM MNs, the first postnatal week is characterized by an increase of the dendritic surface which shows larger dendritic complexity. At the same time, we can observe changes in the membrane passive properties (input resistance and time constant). During the second week, this dendritic complexity gets simplified to values found at birth, the dendritic length increases by the use of the pre-existent membrane, and the action potential diminishes in duration. The simplification and elongation of the dendritic trees is completed during the third postnatal week, and dendrites grow in length, preferably along some spatial axes in order to achieve the dendritic spatial pattern typical of the adult population. Also during the third week, the membrane active properties change: (1) the decrease in duration of mAHP and rheobase (due to a drop in the voltage threshold) are completed; (2) the increase of firing frequency gain started at birth is concluded; and (3) there is an increase of the maximum frequency.

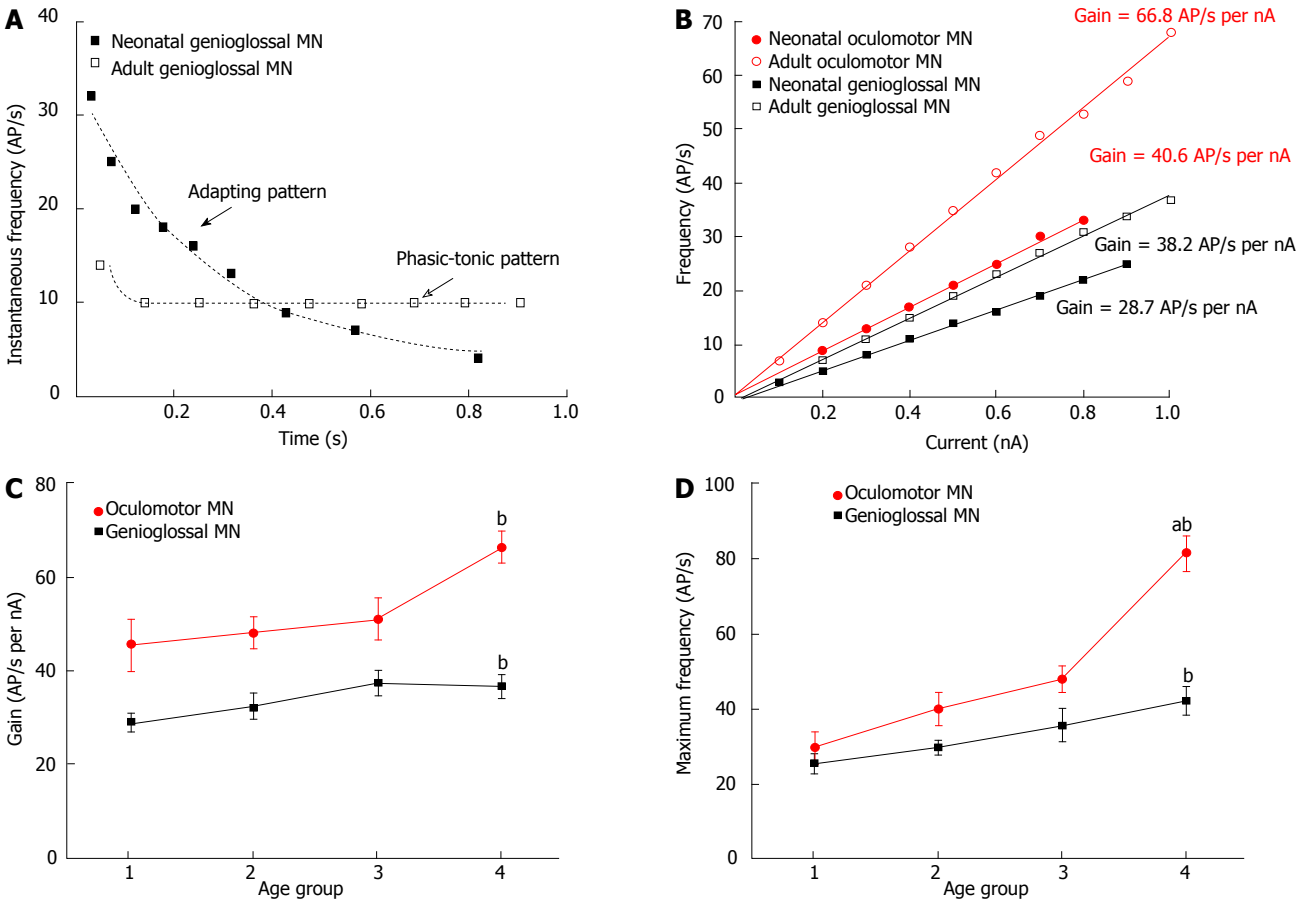

Figure 6 Postnatal maturation of repetitive firing properties of motoneurons from genioglossal and oculomotor nuclei. A: Instantaneous firing frequency evoked by depolarizing current stimulus of 0.3 nA for a representative MN from the GG nucleus. Only the neonatal MN shows an adapting firing pattern while the adult MN shows a phasic-tonic pattern; B: Relationship between current (I) and firing (F) for a representative neonatal MN (filled red circle) and an adult OCM MN (open red circle); and for a representative neonatal MN (filled black square) and an adult MN (open black square). The slope of the I-F relationship is the gain; C, D: Plots illustrating the changes on gain (C) and maximum firing frequency (D) during postnatal development for GG and OCM MNs. Note that gain and maximun firing frequency increase with age, although these increments are larger for OCM MNs. The "a" indicates statistical significance between two consecutive age groups; and the "b" represents statistical significance between age group 1 and age group 4. The age groups 1,2,3 and 4 correspond to P1-P5, P6-P10, P11-P15 and P21-P30, respectively. The data from GG[4] and OCM[10] come from previous studies. MNs: Motoneurons; GG: Genioglossal; OCM: Oculomotor.

TIME WINDOWS IN THE CONTEXT OF DEVELOPMENT OF THE RESPIRATORY AND OCM SYSTEMS

Time windows for changes in membrane properties of MNs are probably determined by extrinsic signals (synaptic inputs and growth factors) related to the circuits in which they participate. The brain-derived neurotrophic factor, when acting through its high-affinity receptor TrkB, has intensively been studied in brainstem neurons during development because of its growth-promoting and trophic effects, including those involved in respiratory control and normal breathing[30,139,140]. It it known that the loss of specific trophic signaling modifies the development of different subpopulations of motoneurons in heterogeneous way[32]. Thus, the lack of cardiotrophin-1[141,142] or IGF-1 significantly reduces the number of brainstem motoneurons[143]. GG and OCM MNs are brainstem motoneurons that innervate tongue and extraocular muscles, respectively. One of the main functional differences between the two muscles lies in the fact that the tongue is present in various motor tasks, including suckling, swallowing and respiration necessary for the animal from the moment they are born, while the extraocular muscles should be ready to work at P21. For example, breathing, which is genetically determined to work at birth, is the result of a well-defined developmental program[144]. This difference in muscle functions could explain the distinct temporal sequences of changes between the two populations of motoneurons studied here. The shortening in action potential duration and mAHP occurs in GG MNs during the first week[4], while the same appears at P15-P20 in OCM MNs[10]. Furthermore, the maximum firing discharge is reached after the third postnatal week in both populations but its increase is much more localized for OCM MNs in the third week[4,10]. Although the evidence is not clear, we could assume that the earliest shortening of the action potential and mAHP in GG MNs correlates with tongue functions that become mature just after birth. The slower frequency of discharge found in newborn MNs is appropriately matched to the slower contraction times found in neonatal skeletal muscles[4,10,145]. The matching of MN

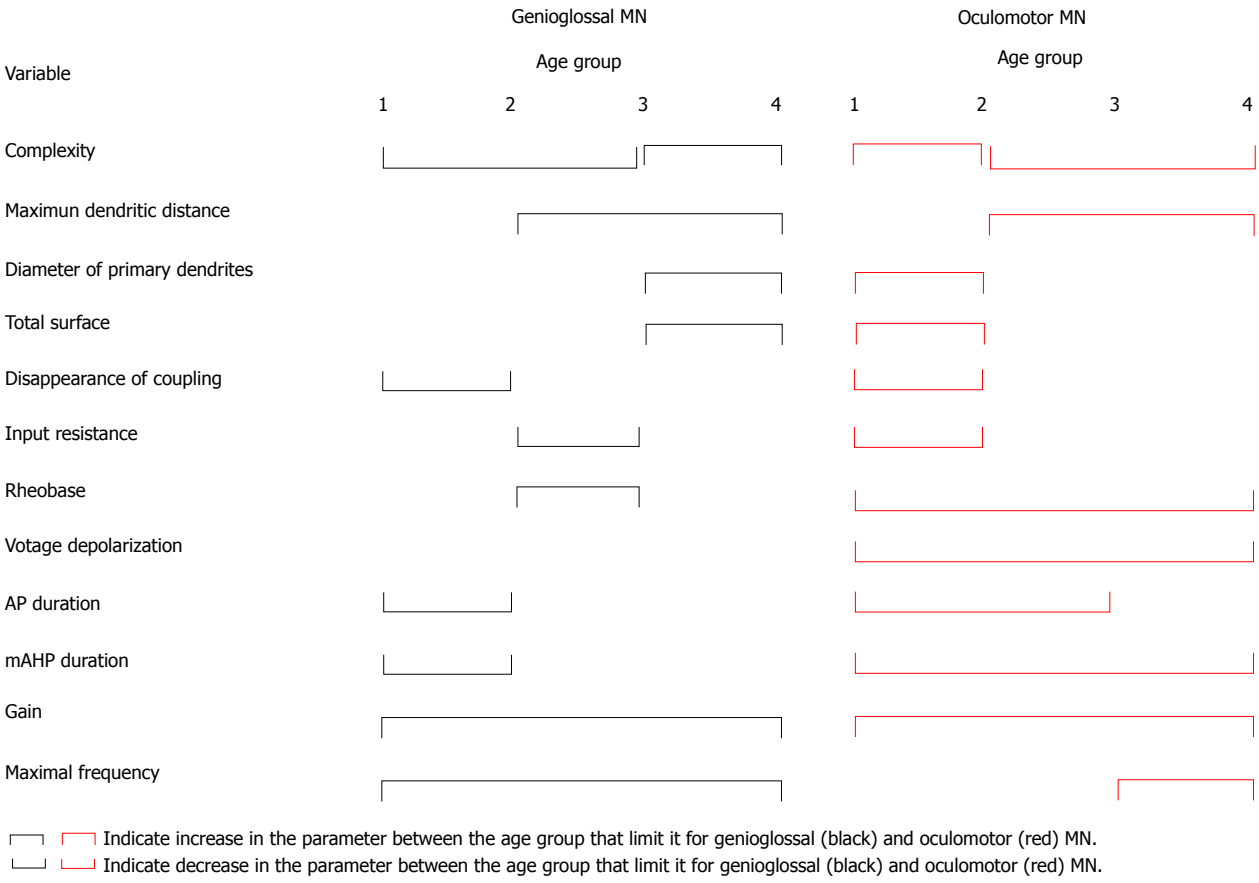

Figure 7 Summary of changes during postnatal periods for genioglossal (black) and oculomotor (red) motoneuron. MNs: Motoneurons.

and muscle properties during postnatal development has been previously described[146,147]. As the speed of respiratory muscle contraction increases with age, the adapting firing pattern is converted to a non-adapting one. This conversion to a faster, non-adapting firing (phasic-tonic pattern) may be required to sustain a fused tetanus of the muscular contraction. Modifications in the maximum firing rate in GG MNs late in development may enable more refined motor functions, and also allow for other tasks including mastication, sneezing, coughing, emesis and "vocalization"[1,2,4,6,148].

The changes described in the reshaping of the dendritic tree and passive membrane properties of GG motoneurons must be understood in the context of the development of respiration in the rat in the first 3-4 weeks of life[4,6]. Respiratory frequencies are characterized by a constant increase with age that reaches peak values at P13 and declines onwards until P21. During the first postnatal week, the absolute tidal volume adopts relative plateau shape, followed by a constant rise until P21[149] denoting the achievement of more mature, deeper, and slower breaths. Furthermore, the second week after birth shows a highly plastic and narrow window of respiratory maturation. This time window is a period in which the neuronal circuits that subserve respiratory control are structurally and/or functionally shaped[150]. These time windows in GG MNs coincide with the decrease in resistance[4], and also with a critical period in the rat (around P12-13) when a functional transient imbalance between excitation and inhibition is found. This imbalance is characterized by a decrease in the amplitude and frequency of excitatory postsynaptic current and an increase in the amplitude and frequency of inhibitory postsynaptic currents[63] as a result of a transient reduced expression of brain-derived neurotrophic factor and TrKB expression[30]. Concurrently with the abrupt fall in brain-derived neurotrophic factor at P12-13, the expression of excitatory neurochemicals (glutamate and NMDA receptor subunit 1) is drastically reduced, whereas that of inhibitory neurochemicals ($GABA_A$, $GABA_B$ receptors and glycine receptors) is significantly enhanced in hypoglossal MNs and in other respiratory-related nuclei[149]. Then, a proliferation of excitatory synaptic inputs must take place later on in order to compensate for the decrease in input resistance and the decrease of excitation to reach threshold. That proliferation of synaptic inputs may be coincident with the increase in surface area that GG MNs exhibit during the third postnatal week[5]. In addition, the lowest values in rheobase are found in GG nuclei at birth[4], and have been understood to ensure the recruitment of most MNs so that suckling movements can be executed, a critical motor task after birth[4,85]. Also for GG MNs, we propose that voltage-gated K^+ channels undergo an increase in number and kinetics during development, and they may be critical determining firing frequency and maximum frequency. The modulation of

these K^+ channels causes genioglossus inhibition due to postsynaptic inhibition of GG MNs in rapid eye movement sleep[151,152], which in turn produces periods of upper airway motor suppression, atonia of the GG muscle, hypoventilation and obstructive apneas. Patency of the upper airway (*i.e.*, tone of the genioglossus muscle) is essential to maintain ventilatory processes during wakefulness as well as nonrapid eye movement (NREM) and rapid eye movement (REM) sleep[152]. Then, defects in maturation patterns in GG MNs may contribute to the development of sleep apnea and other cranial motor disorders including Rett syndrome, and sudden infant death syndrome[149,153].

OCM MNs drive eye movements following vestibular and visual sensory signals[154]. MN excitability, synaptic circuitry and extraocular muscles mature together. However, to establish that the maturation of OCM MNs is driven by a change in both their afferents and extraocular muscles is still to be proved. We may, however, accept that the early developmental processes go along in OCM MNs, vestibular and visual signals and the extraocular muscles they innervate. For example, rodent extraocular muscles are very immature when they are born[155] and their muscle fibers contain supernumerary motor nerve terminals[156]. Maturation in rats has been proven to be ready one week after birth in all vestibular components: the vestibular organ, hair cell sensitivity, and the circuitry that transmits the signal to the vestibular nucleus[157]. Likewise, the circuitry that transmits the signal from the vestibular nuclei to the ocular MNs is ready before P10[157-159]. On the other hand, visual deprivation or lesion to hair cells cause maldevelopment of the extraocular muscles[160,161] and impairment in the vestibulo-ocular reflex[162]. Should visual sensory signals participate in the development of OCM MNs, it would have to be after P12, when the eyelids open. In addition, rodents present eye movements that are evoked by visual and vestibular stimuli from about P21 onwards, although the precision of these reflexes augments later on to achieve clear vision during self-motion[70,71]. Therefore, the maturation of distinct pathways that drive optokinetic and vestibulo-ocular reflexes, including the cerebellar-dependent mechanisms, is ready in the first 3-4 weeks after birth[70]. OCM MNs grow and lower their input resistance with age[9-11,13]. We have found that passive membrane properties mature shortly after birth (P1-P5), while changes in active properties require a longer time scale[10]. Similar findings have been described for vestibular neurons[163] with the conclusion that changes in membrane properties with development happen to enable mature firing properties when required by the proper optokinetic response. The same may apply to the OCM MNs. Eyelids open at about P12 and eye movements evoked by visual and vestibular stimuli occur after the third week after birth[70], when MNs finally present adult firing properties[10,11]. Visual synaptic inputs to MNs may determine recruitment threshold[12,21]. In accordance with this last finding, the decrease in rheobase with age in OCM MNs would guarantee the recruitment of most of these cells after P21, in order to lead to eye movements[9]. With postnatal development, the most active MNs have competitive advantages in muscle synaptic refinement[156]. Extraocular MNs generate burst-tonic activity that enables rapid shifts (saccades) and fixation of the eye orbit[17-19]. Furthermore, muscle derived factors (neurotrophins) are important to ensure neuronal survival during maturation and their range of actions support the phasic and tonic activities of MNs in conducting eye movement[164]. We conclude that lower rheobase and higher maximum frequency of OCM MNs would be needed in the third week of development to generate faster contraction times, shifts (saccades) and fixation of the orbit of the eye[137,138].

CONCLUSION

From our data on GG and OCM MNs[1-13] we conclude that there exists a clear-cut developmental program that produces age-related changes. Common to both populations are modifications in dendritic structure (complexity, length and size), passive properties (input resistance, time constant, and rheobase) and active properties of action potential and firing pattern. However, the time windows of changes in these properties are different and the sequences are even inverted between GG and OCM MNs. Then, most of the described temporal windows of the changes in membrane properties could be understood to be related with the maturation of the respiratory and OCM systems. However, future research in the field would need to address the following issues: (1) how (genetically determined) intrinsic factors shape dendritic branching structure and membrane properties; (2) what processes may be under the control of the targeted muscles, such as motoneuronal survival and electrotonic coupling; (3) how postnatal development of the respiratory and the vestibulo-OCM circuitries determines the dendritic enlargement of dendrites to reach adult territories, as well as changes in passive membrane properties of GG and OCM MNs, respectively; and (4) how active membrane properties of GG and OCM MNs rely on the activation of circuits at the onset of breathing and eye opening.

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