Inhibition: synapses, neurons and circuits

Editorial overview

Gord Fishell and Gábor Tamás

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Gord Fishell

Julius Raynes Professor of Neuroscience and Physiology, NYU Neuroscience Institute, 5th floor, Smilow Research Building, NYU School of Medicine, 522 1st Avenue, New York, NY 10016, USA

Gábor Tamás

Professor of Neuroscience, University of Szeged, Departments of Physiology, Anatomy and Neuroscience, Research Group for Cortical Microcircuits of the Hungarian Academy of Sciences, Kozep fasor 52,

Szeged 6726, Hungary

Function of the nervous system relies on a finely calibrated balance between excitation and inhibition. In this edition the articles focus on inhibition with an eye to their contribution to network function. The topics span the gamut from lineage and genetic specification to whole system approaches. The authors have provided an amazingly diverse sampling of many related topics including circuit assembly, the role of neuromodulators, novel ideas by which inhibition regulates network function, examination of both brain andspinal cord systems, and finally disease. Taken as a whole it shows how far reaching the topic of inhibition in the nervous system has become and should dissuade us from the simple notion that inhibition is simply a matter of dampening excitation to keep the system in check.

Within the cortex, excitation and inhibition develop in parallel. The reviews from Shi, as well as Mueller and Marin explore the relationship between lineage and the cell types they produce. Although ultimately contributing to the same circuits, excitatory pyramidal cells neurons translocate in an orderly fashion to form 'radial units' (Mueller/Marin), while inhibitory interneurons migrate long-distances tangentially to integrate into the same circuits (Mueller/Marin and Shi). Recent lineage studies suggest that not only do lineally related cells clusters aggregate in columns or layers, they may form functional units. While this have been better worked out for excitatory cells, these recent findings argue that sister inhibitory cells may also contribute to same circuits.

Beyond cell lineage, great strides have been made toward understanding the genetic programs initiated in the proliferative zones. Tekki-Kessaris and colleagues review and present an updated version of our understanding of how the basal proliferative zones known as the medial and caudal ganglionic eminences (MGE and CGE, respectively) give rise to interneuron diversity in the forebrain. Their review outlines how our expanding knowledge of transcriptional control, including the recent discovery that *Prox1* acts within CGE-derived is beginning to reveal the genetic underpinnings as to how different interneuron classes are established. As a specific example of how a particular interneuron subtype is generated and

functions, Anderson and colleagues discuss, the Chandelier neuron. This cell type represents not only an uniquely functioning subtype that gates excitatory neuronal output by targeting the initial axon segment but is distinguished by both its late progenitor expression of *Nkx2.1* and perinatal emergence from the MGE. Moreover, given its privileged ability to control neuronal excitation, its function and dysfunction is increasing proving central to both normal brain function and psychiatric disease, respectively.

The question of GABAergic subtype nomenclature is further addressed by Kubota, who provides a concise enumeration of the types of interneuron that have evolved to perform both variable and specific functions. Boundaries of all cell types have not yet been crystallized, however, morphological and functional wiring-properties of non-pyramidal cells are critical for understanding GABAergic functional architecture. In contrast, borders of synaptic junctions were anatomically defined decades ago. However, as Mody points out, effects of GABA are not restricted to synaptic clefts and differences emerge between pyramidal cells and interneurons in the expression of extrasynaptic GABAA receptors, which raises the hope for developing selective modulatory compounds.

In parallel to strides in understanding the specification and classification of different interneuron subtypes, information regarding their early connectivity is beginning to emerge. During development, due to high intracellular chloride levels resulting from low KCC2 expression, inhibitory interneurons can initially be depolarizing. Moreover, as subpopulations of interneurons arise very early in development, they are well positioned to participate in early developmental cortical circuits with Cajal Retzius and subplate neurons, which are transiently present perinatally. Luhmann and colleagues summarize intriguing information suggesting that neural circuits benefit from transient synaptic connections between interneurons and those generated during primary neurogenesis. The significance of such early network assemblies is taken to a new level by Cossart who argues that application of graph theory to information flow in neural circuits leads to the emergence of superconnected hub nodes. Interestingly, only GABAergic neurons were experimentally demonstrated as operational hubs suggesting a critical function in controlling network dynamics.

Indeed, by probing the function of GABAergic neurons *in vivo*, Petersen demonstrates that interneurons contribute to gating sensorimotor integration. Simple behaviors can be associated with the selective reorganization of activity measured in different GABAergic cell populations and network mechanisms underlying cell-type specific related activities are emerging. Capitalizing on novel methodologies, Losoncyexpands this concept toward behavior in showing widespread and cell type dependent involvement of interneurons in working memory, fear learning and discrimination tasks. However, these findings emphasize that although we have unparalleled experimental access to distinct cell types, this must not be mistaken for access to specific synapses.

Network function within the cortex specializes as it matures and the review presented from the Kepecslaboratory discusses how interneurons that subserve specific functions contribute to this specialization. Complementing this piece, is one from the Buzsaki laboratory that explores the intriguing insights that have come from our newly developed abilities to record form large numbers of cells *in vivo* and to optogenetically manipulate them during normal behaviors.

Going from the multicellular vantage to that of specific neuromodulators, the Rudy and Castillo laboratories discuss how specific neuromodulators alter the function of GABAergic

interneurons, as well as the circuits they contribute to. Rudy and colleagues delve into the actions of acetylcholine, which despite its widespread innervation can have remarkably specific and apposing actions on different cell types, in some cases concurrently. Similarly Castillo and colleagues, examine cannabinoid signaling and show that its actions depend on activity, such that the action of cannabinoids is distinct during phasic and tonic modulation. Furthermore, cannabinoids have a role in regulating synaptic plasticity, which may relate to burgeoning evidence of their involvement in psychiatric disease.

In addition to neuromodulation that can alter inhibitory neuron recruitment, GABA itself can function in new and unexpected ways. In addition to spillover from the release sites, GABA can mediate widespread action in a variety of ways. One of these, termed blanket inhibition by Yuste, originates from a handful of interneuron populations forming dense innervation of pyramidal cells without preference for individual postsynaptic neurons. Selection of activity patterns is posited to be mediated by disinhibitory interneurons making holes in the dense inhibitory 'blanket'. Bacci provides further insight on disinhibition focusing on self-innervation of interneurons and suggests that autaptic transmission serves a dual role in promoting network synchronization with single spikes or favoring desynchronization of population activity through high-frequency firing. An alternative way that widespread inhibitory action can be achieved is put forward by McBain, who suggests that it can be mediated through GABAB receptors. Recent work implicates that these metabotropic receptors in an unconventional manner mediate rapid termination of persistent network activity in the cortex. The findings suggest they inhibit the firing of principal cells by acting on voltage-gated calcium channels perhaps when subsets of layer 1 interneurons are recruited by subcortical or long range corticocortical inputs.

Our mechanistic understanding of insults to the brain, to a large extent, is based on observations concerning excitatory/inhibitory balance. However, Kaila emphasizes that major imbalances are unlikely to explain infrequent and unpredictable seizures in chronic epileptics. The work they present demonstrates that context-specific and age-specific actions of GABAA receptors or intracellular signaling functioning down-stream of TrkB receptors may prevent or promote epileptogenesis. The function of identifiedGABAergic cell types is discussed by Lewis in connection with schizophrenia. A potential link involving potassium channels is proposed to link impaired gamma frequency oscillations, elements of development of parvalbumin-containing interneurons and the molecular alterations detected in individuals with schizophrenia.

Beyond their role in higher brain structures, interneuron function is prominent. Copogna and colleagues demonstrate this by examining the basal lateral amygdala, a region whose structural organization while resembling the cortex is uniquely specialized with regard to its neurological actions. Copogna illustrates this by discussing evidence that interneurons within the baslateral amygdala are tightly phase locked with the local networks they contribute to, an observation that will likely have functional consequences as the circuits in this structure are better understood.

In the papers by Fidelin and Wyart, as well as the review by Goulding, the focus shifts from anterior neural structures to those that form the servo-mechanic function of the nervous system. Their analyses of the spinal cord highlights how interneurons contribute to local recurrent spinal circuits, as well as those that regulate central pattern generation, which is essential to movement. What makes comparison of these two reviews so exciting is both their use of cutting edge genetic tools and the similarities and differences gained from examining

two distinctly different genetic systems. The Goulding review with its focus on mice provides us with an exquisite matching of cell types to function and yields insights that have immediate relevance to the analogous circuits in humans. The Fidelin and Wyart review ultilizes optogenetic methods to identify and manipulate specific spinal circuits. Together, from these cross species approaches one gains an appreciation of the varied and subtle contributions of inhibition to locomotion.

Clearly the study of interneurons and more generally inhibition is increasingly impacting the way we think about how the nervous system functions. Of the many topics covered in this issue, it is notable that each of these areas is rapidly expanding and bewildering in the directions it might take us. Indeed, these opinion pieces paint the outlines of a broad tapestry that suggests how further studies of inhibition will shape our ideas of nervous system function and how to probe, manipulate and ultimately repair it.

Vitae

Gord Fishell is the Julius Raynes Professor of Neuroscience and Physiology at NYU School of Medicine and the associate director of the NYU Neuroscience Institute. His laboratory is interested in using molecular genetic approaches to study how cortical interneuron diversity in mammals is generated and how specific subtypes of these neurons functionally integrate into the cerebral cortex during development. He was briefly an assistant professor at the Rockefeller University and then took a position in the NYU's Developmental Genetics program at the Skirball Institute. Since establishing his own laboratory, Dr. Fishell has studied how GABAergic interneurons are specified and integrate into the brain. Present work in the laboratory centers around examining how laminar and areal position within the cerebral cortex influences the connectivity of particular cortical interneuron subtypes. This work has led his laboratory to study the mechanisms by which interneurons establish their obligate contacts with the principal excitatory pyramidal neurons, a process that increasingly appears to rely on local activity-dependent cues.

Gábor Tamás completed his PhD with Peter Somogyi and identified the number and position of synapses between neocortical neurons. His group found that neurogliaform cells elicit slow inhibition in the cortex and showed that apart from being inhibitory, axo-axonic cells might serve as the most powerful excitatory neurons. His current work is concerned with in depth molecular analysis of identified interneurons and subsequent functional analysis of novel marker genes at the cellular and network level in human and rodent cortices.