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ANALYSIS OF IDENTIFICATION OF GENES REGULATING GABAERGIC CORTICAL INTERNEURON MATURATION

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Abstract:

Interneurons play a vital role in the wiring and circuitry of the developing nervous system of all organisms, both invertebrates and vertebrates alike. Generally speaking, an interneuron is a specialized type of neuron whose primary role is to form a connection between other types of neurons. The basic aim of the study is identification of genes regulating GABAergic cortical interneuron maturation. Fast GABAergic responses are mediated by $GABA_A$ receptors, chloride-permeable pentameric channels composed of an assembly of subunits from eight classes of subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3). Although receptor composition differs across neuronal subtypes, subunits most often assemble with a 2α:2β:γ stoichiometry. It is estimated that there are over 20 different subtypes of GABAergic interneurons in the cortex, and subtypes are also distinguished from one another based upon the calcium-binding proteins they express, which serve as markers. It is concluded that there is an extensively studied transcriptional network that plays a role in regulating proper development and specification of MGE-derived GABAergic cortical interneurons

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INTRODUCTION:

Interneurons play a vital role in the wiring and circuitry of the developing nervous system of all organisms, both invertebrates and vertebrates alike. Generally speaking, an interneuron is a specialized type of neuron whose primary role is to form a connection between other types of neurons. They are neither motor neurons nor sensory neurons, and also differ from projection neurons in that projection neurons send their signals to more distant locations such as the brain or the spinal cord. Of great importance is that interneurons function to modulate neural circuitry and circuit activity.

During embryonic development, GABAergic interneurons, a main inhibitory component in the cerebral cortex, migrate tangentially from the ganglionic eminence (GE) to cerebral cortex. After reaching the cerebral cortex, they start to extend their neurites for constructing local neuronal circuits around the neonatal stage. Aberrations in migration or neurite outgrowth are implicated in neurological and psychiatric disorders such as epilepsy, schizophrenia and autism. Previous studies revealed that in the early phase of cortical development the neural population migrates tangentially from the GE in the telencephalon and several genes have been characterized as regulators of migration and specification of GABAergic interneurons. However, much less is known about the molecular mechanisms of GABAergic interneurons-specific maturation at later stages of development. Here, we performed genome-wide screening to identify genes related to the later stage by flow cytometry based-microarray (FACS-array) and identified 247 genes expressed in cortical GABAergic interneurons.

GABAergic interneurons are the only source of GABA and the main source of inhibition in the mammalian central nervous system. Depending on the brain region, they constitute 10%–25% of the total number of cortical neurons, where they play a crucial role in controlling and orchestrating the activity of pyramidal neuron assemblies. GABAergic interneurons are extremely diverse in their morphology and functional properties. At least 20 different cortical subtypes and 21 hippocampal subtypes have been identified.

Interneurons can be broadly classified according to at least six different criteria: (1) morphology of soma and axonal and dendritic arbors; (2) molecular markers including but not restricted to calcium binding proteins (parvalbumin, calbindin, calretinin), neuropeptides (e.g., Vasoactive Intestinal Peptide [VIP], neuropeptide Y [NPY], reelin, somatostatin), and receptors (e.g., $5HT_3R$, mGluR1, CB1); (3) postsynaptic target cells/subcellular compartments; (4) area of origin and transcription factors involved in subtype fate determination; (5) intrinsic physiological properties; and (6) function in the adult brain. Since there is not a complete correspondence between the different classifications, it has remained a challenging task to come up with a classification spanning all categories and this is still an issue of debate.

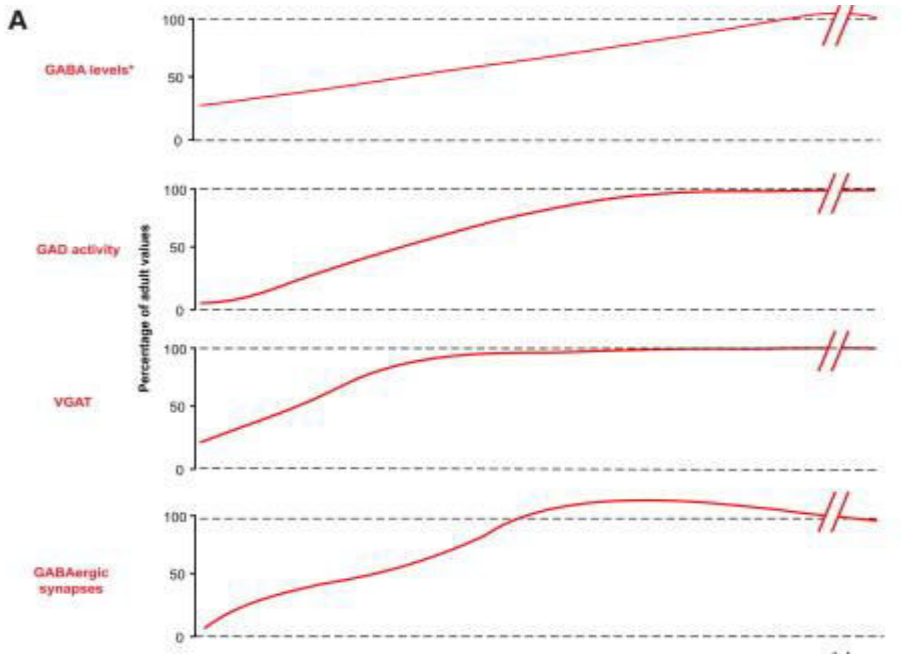

Figure 01: Maturation of GABAergic Neurotransmission

Objectives of the study

The basic aim of the study is identification of genes regulating GABAergic cortical interneuron maturation. This review will place an emphasis on the function and origin of GABAergic cortical interneurons of the developing nervous system. Within the overarching categorization of GABAergic interneurons there are also numerous interneuron subtypes that are largely categorized based on the surface markers they express.

Role of GABAergic cortical interneurons

Given that the population of GABAergic interneurons in the brain is such a heterogeneous one, it is only logical that the many different classes of interneurons will have a myriad of roles to play in the adult nervous system. GABAergic neurons play an inhibitory role and synaptically release the neurotransmitter GABA in order to regulate the firing rate of target neurons. Neurotransmitter release typically acts through postsynaptic $GABA_A$ ionotropic receptors in order to trigger a neuronal signaling pathway.

This research field typically organizes interneuron role/function into three components: (1) afferent input, (2) intrinsic properties of the interneuron, and (3) targets of the interneuron. Generally speaking, interneurons receive input from various sources, including pyramidal cells as well as cells from other cortical and subcortical regions. With regard to output, cortical interneurons engage in feed-forward and feedback inhibition. Regardless of the mode of output, the cortical interneuronal network is further complicated by the fact that a single cortical interneuron is capable of making multiple connections with its excitatory neuronal target.

Maturation of GABA Receptors in Interneurons and Pyramidal Cells

Fast GABAergic responses are mediated by $GABA_A$ receptors, chloride-permeable pentameric channels composed of an assembly of subunits from eight classes of subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3). Although receptor composition differs across neuronal subtypes, subunits most often assemble with a 2α:2β:γ stoichiometry. The $GABA_A$ reversal potential (E_{GABA}) is primarily determined by the chloride reversal potential of the cell (E_{Cl}). E_{Cl} depends on the intracellular chloride concentration, which is set by the opposite action of the chloride cotransporters NKCC1 and KCC2 that are involved in chloride uptake and extrusion, respectively. In the immature brain, KCC2 expression in most neurons is delayed compared to NKCC1 expression, resulting in chloride accumulation in the cytoplasm and an E_{GABA} greater than resting membrane potential. As a consequence, GABA is depolarizing in most immature neurons, at least in acute brain slices. KCC2 expression in the forebrain begins around the end of the first postnatal week and renders GABA hyperpolarizing. Neuronal precursors express $GABA_A$ receptors from very early stages onward in the immature brain. In rodents, $GABA_A$ receptors are present in neuronal stem cells well before the formation of GABAergic synapses. The composition of $GABA_A$ receptors in cortical neurons changes during the course of neuronal maturation. In the rat brain, the expression of α3, α5, and β3 mRNAs starts at late embryonic stages and peaks during early postnatal development. As the transcription of these three genes decreases, expression of α1, α4, β2, and δ gradually increase during postnatal development in cortical neurons. These subunits are predominant in the adult brain, together with α2 and γ2, whose expression remains fairly constant throughout development. The developmental change of $GABA_A$ receptor subunit expression is paralleled by the decrease in the decay time constant of GABAergic IPSCs (τ_{IPSC}).

RESULTS:

It is estimated that there are over 20 different subtypes of GABAergic interneurons in the cortex, and subtypes are also distinguished from one another based upon the calcium-binding proteins they express, which serve as markers. Studies performed in both mouse and rat brain tissue have suggested that in particular, the calcium-binding protein known as parvalbumin, and the neuropeptide somatostatin, are two crucial markers in defining the most predominant interneuron subtypes within the cerebral cortex. Importantly, the PV-expressing interneuron population is independent from the SST-expressing population, in that expression of these markers does not overlap. In addition to PV- and SST-positive GABAergic interneurons, which together comprise approximately 70% of the total GABAergic cortical interneuron population, another subgroup of interneurons that express 5HT3aR were found to comprise approximately 30% of all interneurons? While these three interneuronal subpopulations account for nearly (if not all) 100% of all GABAergic cortical interneurons, it is also important to remember that each of these populations, especially the 5HT3aR-expressing population, is heterogeneous, and therefore expresses other proteins or neuropeptides that contribute to their characterization.

Table 1: GABAergic cortical interneuron subtypes

Marker	% Total GABA + Population	Morphology	Axonal targeting	Firing pattern	Origin
Parvalbumin (PV)	40	Basket cells	Proximal dendrites/soma	Fast-spiking	Ventral MGE
		Chandelier cells	Axonal initial segment		
Somatostatin (SST)	30	Martinotti cells	Distal dendrites	Bursting	Dorsal MGE
5HT3aR	30	VIP+: Small bipolar	Proximal dendrites	Irregular-spiking,	CGE
		VIP-: Neurogliaform cells	Other GABA neurons	Fast-adapting	
				Late spiking accommodating	

DISCUSSION:

In the recent years there has been a push to create a consistent nomenclature for the varying interneuronal subtypes; a 2005 conference in Petilla, Spain, was held to accomplish this task. A group of researchers known as the Petilla Interneuron Nomenclature Group (PING) convened to formulate a set of terminologies to describe the morphological, molecular, and physiological features of GABAergic cortical interneurons. Morphologically speaking, cortical interneurons are described with regard to their soma, dendrites, axons, and the connections they make. Molecular features include transcription factors, neuropeptides, calcium-binding proteins, and receptors these interneurons express, among many others. Physiological characteristics include firing pattern, action potential measurements, passive or subthreshold parameters, and postsynaptic responses, to name a few. The overarching goal of this conference and the resulting Petilla terminology is to create a uniform set of criteria by which interneurons can be described so as to reduce confusion between the findings by various research groups in this field.

CONCLUSION:

It is concluded that there is an extensively studied transcriptional network that plays a role in regulating proper development and specification of MGE-derived GABAergic cortical interneurons.

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