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Review

Homeostatic activity-dependent paradigm for neurotransmitter specification

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Abstract

Calcium-signaling plays a central role in specification of the chemical transmitters neurons express, adjusting the numbers of cells that express excitatory and inhibitory transmitters as if to achieve homeostatic regulation of excitability. Here we review the extent to which this activity-dependent regulation is observed for a range of different transmitters. Strikingly the homeostatic paradigm is observed both for classical and for peptide transmitters and in mature as well as in embryonic nervous systems. Transmitter homeostasis adds another dimension to homeostatic regulation of function in the nervous system that includes regulation of levels of voltage-gated ion channels, densities of neurotransmitter receptors, and synapse numbers and strength.

Keywords: Homeostatic activity; Calcium-signaling; Neurotransmitter receptors

Contents

1. Introduction

Homeostatic regulation of neural activity is a process that prevents individual neurons and neural circuits from becoming hyper- or hypoactive. This is an essential process for the continued function of the nervous system, because experience-dependent plasticity would otherwise bias neurons and networks out of their operating range. A number of mechanisms have been shown to act as stabilizers of neuronal and network activity. The densities of voltage-gated ion channels and postsynaptic receptors, presynaptic transmitter release or reuptake, global regulation of synaptic strengths throughout a neuron and the number of functional synapses have been shown to be modulated to contribute to homeostasis [1]. In this review we expand the boundaries of activity-dependent changes by including the choice of neurotransmitter neurons express, i.e. switching from an excitatory to an inhibitory transmitter or vice versa, in a homeostatic way.

Specification of the neurotransmitters synthesized and released by neurons is a significant step in their differentiation. The appearance of the appropriate transmitters is essential

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for communication of neurons with their postsynaptic targets, expressing cognate receptors. If inappropriate transmitters are expressed, communication with postsynaptic neurons is anticipated to fail and neurons are expected to be isolated from their circuits. Experimental evidence has demonstrated genetic regulation of this aspect of development, but electrical activity and calcium (Ca^{2+}) influx also play a key role. Here we summarize investigations of the role of activity in transmitter specification, assembling evidence from studies of classical and peptide transmitters and from embryonic and mature nervous systems that suggests that the role of activity in transmitter specification is geared toward homeostasis. We identified studies in which increases or decreases in activity changed either the number of neurons expressing a particular transmitter or the transmitter expressed in a population of neurons. Knowing whether the transmitter initially expressed was excitatory or inhibitory, we found that the changes in transmitter specification were consistent with a homeostatic paradigm. This may be a general feature of the organization of the nervous system, whereby activity shifts transmitter specification towards excitation or inhibition as if to achieve a constant level of excitability. We elaborate a model that reconciles the roles of genetic programs and activity in neurotransmitter specification in the context of homeostasis of excitability.

2. Embryonic development

2.1. Classical transmitters

The classical neurotransmitters expressed in differentiating populations of neurons have been shown to be regulated genetically by transcription factors and electrically by Ca^{2+} influx. Specification of acetylcholine (ACh) by transcription factors has been demonstrated by ectopic expression in the chick spinal cord, leading to inappropriate expression of this transmitter in interneurons [2,3]. However, Ca^{2+} signaling regulates neurotransmitter specification in other systems. Depolarization or neuronal activity generating Ca^{2+} influx suppresses cholinergic differentiation of cultured neonatal rat superior cervical ganglion neurons in response to a factor in conditioned medium and stimulates adrenergic differentiation. Blocking Ca^{2+} influx leads to an increased incidence of cholinergic neurons and reduction of the adrenergic phenotype [4]. Suppression of Ca^{2+} elevations in cultured embryonic rat hypothalamic neurons, by blockade of NMDA receptors, L-type voltage-gated Ca^{2+} channels, or intracellular BAPTA to chelate Ca^{2+}, enhances expression of the cholinergic phenotype in these neurons but not in neurons cultured from the cerebral cortex [5]. Suppression of the activities of Ca^{2+}-calmodulin II/IV or protein kinase C produces similar results, arguing that these Ca^{2+}-dependent enzymes are part of the signal transduction pathway.

Specification of the neurotransmitter γ-aminobutyric acid (GABA) by transcription factors is demonstrated by loss-of-expression and gain-of-expression experiments, which lead to loss or gain of expression of this transmitter [6,7]. In other systems Ca^{2+} transients and electrical activity regulate expression of GABA. The incidence of expression of GABA and its synthetic enzyme, glutamic acid decarboxylase (GAD), are upregulated in cultured embryonic *Xenopus* spinal neurons by increasing frequencies of Ca^{2+} spikes mimicking endogenous spontaneous activity in vitro [8,9]. Experimentally induced changes in the frequency of global Ca^{2+} transients are positively correlated with the onset of GABAergic neurotransmitter phenotype embryonic mouse neural precursors [10]. In a parallel manner, neuronal activity increases GAD 65 and GAD 67 expression in organotypic cultures of postnatal rat visual cortex. Suppressing activity at early times in vitro decreases both mRNA and protein levels of GAD 65 and 67, which recover when activity is allowed to resume; mRNA and protein levels are resistant to late-onset activity deprivation [11].

Specification of dopamine (DA) expression follows a paradigm of co-regulation by transcription factors and activity. The dopaminergic phenotype is normally detected in 10–20% of rat sensory petrosal ganglion neurons. High concentrations of KCl or application of veratridine, which increases neuronal activity, induce TH expression in 100% of cultured embryonic neurons, with a substantial increase in DA content. TH levels remain elevated in a subset of neurons, implying a change in transmitter phenotype in these cells [12]. Depolarization increases the proportion of dopaminergic neurons in nodose, petrosal and dorsal root sensory ganglia. This activity-dependent expression parallels the temporal pattern of dopamine expression in vivo, producing large increases in dopaminergic embryonic neurons and smaller ones postnatally, via Ca^{2+} influx through voltage-gated Ca^{2+} channels [13]. Significantly, patterned electrical stimulation of petrosal ganglion neurons in vitro induces TH expression [14] and physiological stimulation of these neurons in vivo induces TH expression exclusively in cells expressing Phox2a/2b transcription factors (Fig. 1; [15]). The timing of appearance of these transcription factors is correlated with the ability of petrosal ganglion neurons to express TH. DA released by neurons of the petrosal ganglion acts as an inhibitory transmitter, reducing the excitatory postsynaptic currents of neurons of the nucleus tractus solitarius [16]; electrical activity and elevation of Ca^{2+} increase the number of neurons in which it is expressed. Observation that the appearance of the dopaminergic phenotype in rat olfactory bulb neurons depends on afferent innervation both in vitro and in vivo is consistent with homeostatic activity-dependent specification of neurotransmitter expression [17].

Interestingly, activity and Ca^{2+} elevations appear to exert opposing effects on the expression of excitatory and inhibitory transmitters. Suppressing Ca^{2+} influx leads to increases in the incidence of neurons expressing ACh and decreases in the numbers of neurons expressing GABA or DA. In contrast, enhancing Ca^{2+} influx leads to decreases in the numbers of neurons expressing ACh and increases in the in-

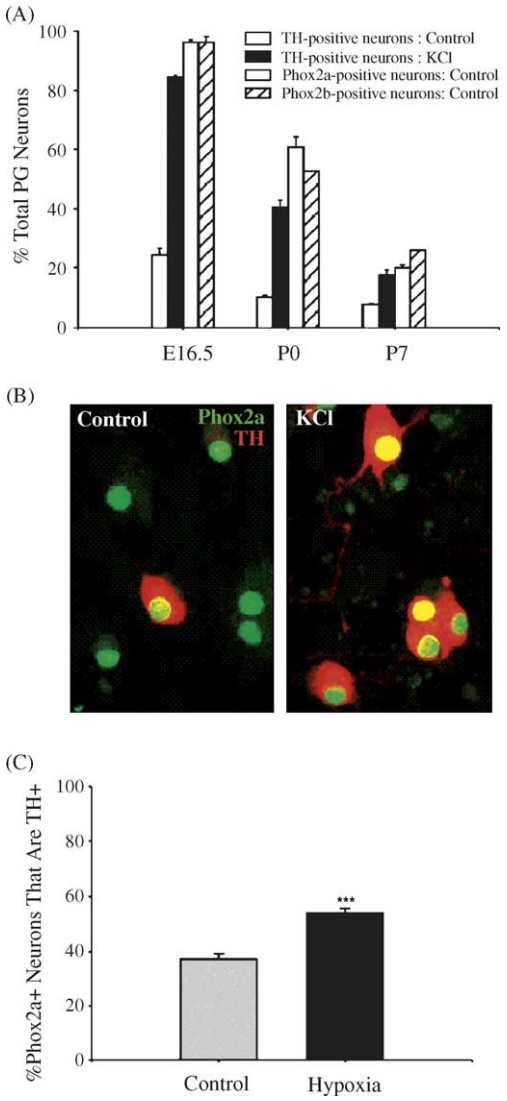

Fig. 1. Activity-dependent specification of dopamine in ganglionic neurons in vitro and in vivo. (A) Developmental time course of Phox2a, Phox2b and depolarization-induced tyrosine hydroxylase (TH) expression in culture. Petrosal ganglia were removed at the ages indicated and grown in dissociated cell culture for 3 days in the absence (control) or presence of 40 mM KCl (KCl). Data are mean ± S.E.M. (B) Images illustrating nuclear Phox2a expression and cytoplasmic TH expression in E16.5 cultures grown as in (A). (C) Effects of hypoxia, stimulating petrosal ganglion neurons, on TH expression in neurons expressing Phox2a. Newborn rats were exposed to 12% hypobaric hypoxia for 1 week from birth and sections of petrosal ganglia from p7 animals were immunostained for Phox2a and TH. Data are mean ± S.E.M. (*** $P \leq 0.001$; after [15]).

cidence of expression of GABA or DA. The results suggest that the numbers of neurons expressing a particular transmitter may be regulated in such a way as to maintain a steady level of excitability in the nervous system.

Recent work reveals that activity-dependent specification of transmitter expression is a prominent feature of differentiation of spinal neurons in *Xenopus* embryos. Moreover the process appears directed to homeostatic regulation of excitability, extending earlier findings that suggest such regulation [18]. This study identified characteristic signatures of spontaneous Ca^{2+} spikes for four of the eight classes of neurons in the embryonic neural tube during a 10 h period of development following neural tube closure. Spikes, which result from Ca^{2+}-dependent action potentials and Ca^{2+}-induced Ca^{2+}-release, are generated aperiodically at low frequencies ($1–20\ h^{-1}$), and are stereotyped for different neuronal classes. Normal differentiation of these four types of neurons produces glutamatergic sensory neurons, cholinergic motoneurons, and glycinergic and gabaergic interneurons.

Altering the patterns of Ca^{2+} spikes in vivo leads to changes in the neurotransmitters expressed by these spinal neurons. Suppression of activity, by overexpressing inward rectifier potassium channels or by local delivery of Ca^{2+} and Na^{+} channel blockers, leads to increased incidence of expression of excitatory transmitters, ACh and glutamate, and to decreased incidence of expression of inhibitory transmitters GABA and glycine. In contrast, enhancement of activity by overexpression of Na^{+} channels or local delivery of veratridine generates an increased number of neurons expressing inhibitory transmitters and a decreased number of neurons expressing excitatory transmitters. Remarkably, following enhancement of Ca^{2+} spike activity, some sensory neurons are no longer glutamatergic and some motoneurons are no longer cholinergic; instead, these neurons acquire GABAergic or glycinergic phenotypes. These results suggest that Ca^{2+} spike activity drives homeostatic specification of neurotransmitters, as if to ensure a balance of excitability.

Homeostasis must be achieved by a feedback loop that signals the level of electrical activity in the neurons. However, this feedback loop does not involve transmitter release associated with synaptic connections among neurons in the neural tube, because homeostasis occurs when neurons are grown in low density dissociated cell cultures free of synaptic connections. Under these conditions, suppression and enhancement of Ca^{2+} spike activity continue to specify homeostatic expression of excitatory and inhibitory transmitters. These results raise the possibility that a feedback loop involving spontaneous release of transmitters [18] is cell autonomous, with transmitters activating receptors on the neurons from which they are released. This work led to a model in which expression of transcription factors programs the expression of ion channels that generate Ca^{2+} spikes, which in turn drive expression of transcription factors that program the activation of genes encoding proteins that regulate transmitter metabolism (Fig. 2). Future analysis of homeostasis will focus on Ca^{2+} spike-dependent release of molecules that could act automatically or on a wholly intracellular signaling process.

How is information encoded by the pattern of Ca^{2+} spikes? Imposition of Ca^{2+} transients closely mimicking spontaneous Ca^{2+} spikes with respect to waveform and frequency reveals that the incidence of gabaergic neurons is directly proportional [8,9] while the incidence of cholinergic and glutamatergic neurons is inversely proportional to the frequency of periodic spikes [18]. However, this pattern of stimulation results in coexpression of glutamate and ChAT and fails to

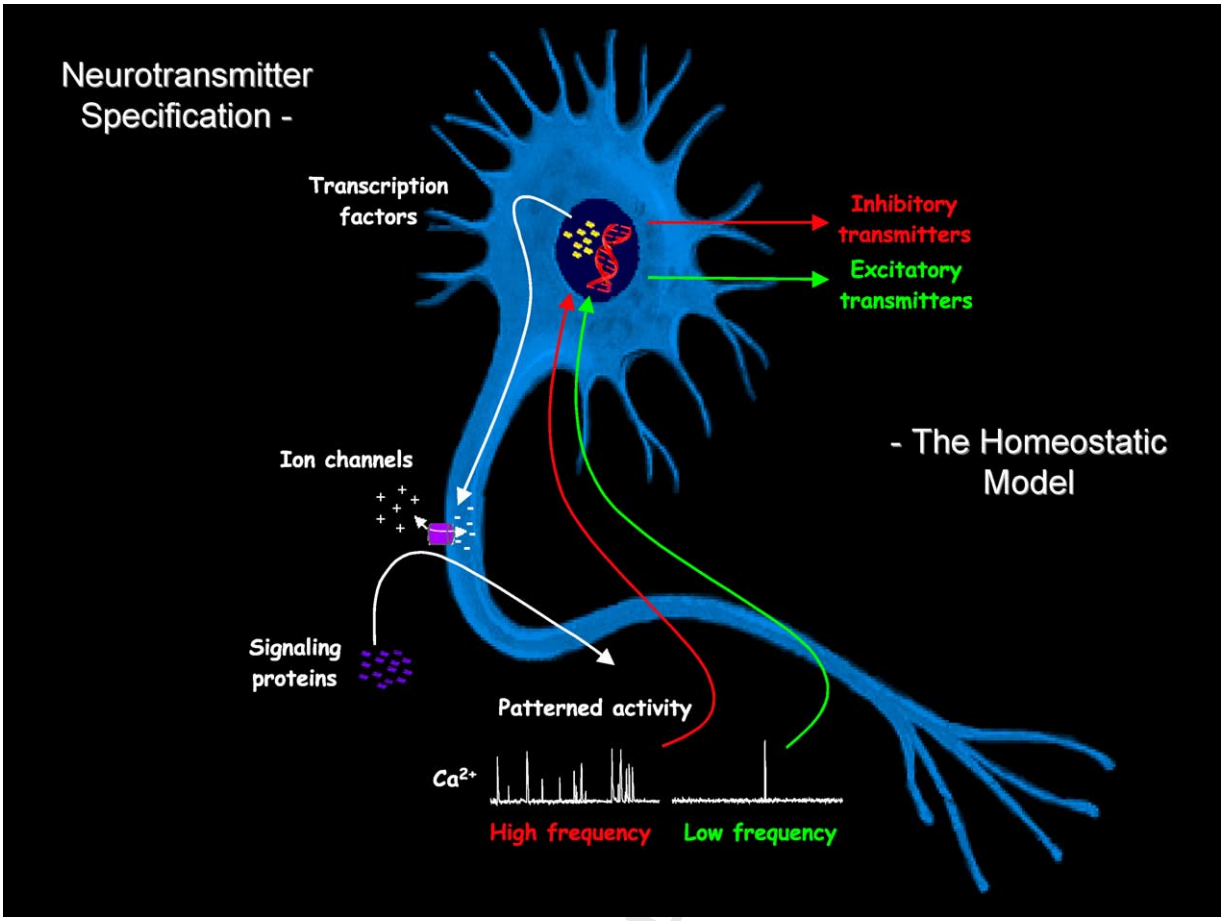

Fig. 2. Model for neurotransmitter specification. Expression of transcription factors identifies classes of neurons that express constellations of ion channels. These channels produce patterned Ca^{2+} spike activity that is modulated by signaling proteins. Patterns of spike activity, activating Ca^{2+}-dependent transcription factors, regulate expression of transcripts encoding the enzymes that synthesize and store specific transmitters. Different levels of activity homeostatically specify expression of excitatory and inhibitory transmitters (after [35]).

reproduce the largely one-to-one expression of a single classical transmitter in a single class of neurons in vivo. Periodic stimulation patterns may not adequately reproduce the natural, aperiodic spike patterns, or additional factors may be required to achieve the expression of a single transmitter in single class of neurons.

2.2. Peptide transmitters

Does regulation of peptide transmitter expression obey the principle of homeostasis similar to that of classical transmitters? Do depolarization and Ca^{2+} influx lead to increased incidence of expression of inhibitory peptide transmitters and decreased incidence of expression of excitatory peptide transmitters? Somatostatin (SS) is an inhibitory transmitter in the hippocampus [19,20]. Blocking inhibitory or excitatory activity in postnatal rat slice cultures of hippocampal interneurons with bicuculline or CNQX increases and decreases, respectively, the number of SS-immunoreactive neurons (Fig. 3; [21]). These results indicate that the extent of expression of SS in maturing hippocampal interneurons is homeostatically tuned to the endogenous balance of excitatory and inhibitory activity.

Substance P (SP) can act as an inhibitory transmitter [22,23]. In the visual system, innervation by retinal ganglion cell terminals precedes the expression of substance P (SP) by *Rana* tectal cells, and transection of the optic nerve results in a decrease in SP expression in the tectal lobe in tadpole [24], consistent with homeostatic regulation. Blocking glutamate receptors with CNQX or AP5 in vivo does not affect nerve-dependent regulation of the SP population of cells in the developing optic tectum, but neurotrophin-4/5 produces increases in SP in normal animals and prevents the effects of optic nerve transection [25]. Whether or not NT-4/5 affects the activity of these neurons as it does in cultured mesencephalic dopamine neurons [26] remains to be determined.

3. Mature regulation

Intriguingly, homeostatic activity-dependent specification of neurotransmitter expression appears not to be confined to

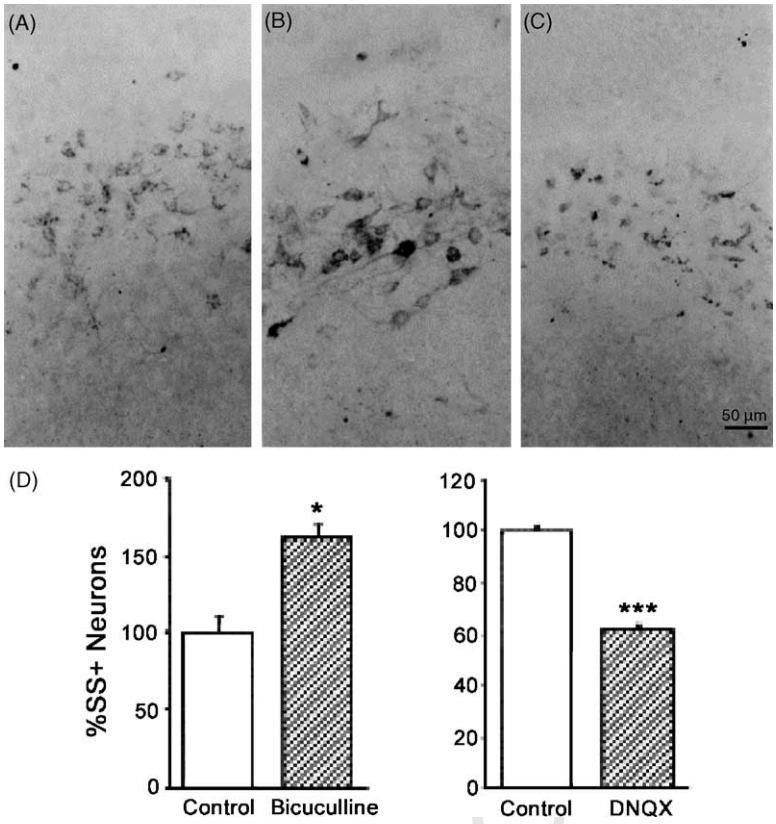

Fig. 3. Activity-dependent specification of somatostatin in slices of the striatum. Effects of bicuculline or DNQX treatment on somatostatin immunoreactivity in neurons of the striatum oriens. (A) Control slice. (B) Bicuculline-treated slice. (C) DNQX-treated slice. Staining increases in intensity after bicuculline treatment and decreases following treatment with DNQX. Scale bar is 50 μm. (D) Quantitation of changes in somatostatin-positive neurons. Bicuculline induced a 60% increase in the number of labeled cells while DNQX induced a 40% decrease in the number of labeled cells (after [21]).

the developing nervous system. In the adult frog optic tectum SP expression is suppressed by blockade of ACh receptors with mecamylamine, consistent with decreased excitation leading to decreased expression of an inhibitory transmitter [27]. Substantial evidence has been obtained for homeostasis involving glutamate and GABA expression in the adult CNS. Although high frequencies of Ca^{2+} spikes generated in pediatric epilepsy may be detrimental to brain development [28], seizure activity appears to regulate expression of neurotransmitter homeostatically to suppress this activity. Mossy fibers normally generate excitatory glutamatergic postsynaptic potentials on rat hippocampal CA3 pyramidal cells, but seizures induce glutamatergic and GABAergic cotransmission [29] that coincides with upregulation of transcripts encoding GAD 67 and the vesicular GABA transporter in the dentate gyrus and mossy fibers. Stimulation of the dentate gyrus to potentiate synaptic responses without inducing seizures leads to the appearance of fast bicuculline-sensitive inhibitory postsynaptic potentials (ipscs) in a process that is blocked by the protein synthesis inhibitor, cycloheximde [30]. GABAergic transmission from mossy fibers is normally present in the 3–5-week old guinea pig [31]. Investigation of neonatal rat hippocampus reveals that a GABAergic input is normally present until 3 weeks of age, after which activation of granule cells no longer evokes synaptic responses in CA3 in the presence of glutamatergic antagonists [32]. The change in electrophysiological assessment is supported by immunocytochemical analysis of GABA and GAD 67 expression; RT-PCR demonstrates downregulation of vesicular GABA transporter transcripts in the adult.

The levels of GABA and GAD protein also appear to be regulated by physiological activity in the visual cortex of young adult monkeys [33]. Monocular deprivation, tetrodotoxin injection or eyelid suture, which reduce the patterned input to the visual cortex, all decrease the number of GABA and GAD-immunoreactive neurons in the deprived regions, in some cases by as much as 50%. This effect is not accompanied by cell death and is fully reversible. In what may be a similar process, schizophrenic patients with functional hypoactivity of the dorsolateral prefrontal cortex exhibit reduced expression of GAD transcripts relative to matched controls, with no significant reduction in the number of neurons [34]. Cell migration and survival appear to be within the range of normal. The results are consistent with activity-dependent downregulation of transmitter-related gene expression associated with adult onset of schizophrenia, but a role of developmental suppression of activity is not excluded. It is not known whether the incidence of glutamatergic neurons in-

Table 1
Specification of neurotransmitters in a range of embryonic and mature neurons is regulated by neuronal activity

Transmitter	Tissue	Stage	Citations
Acetylcholine	Sympathetic ganglion	Embryonic	[4]
	Hippocampus	Embryonic	[5]
	Spinal cord	Embryonic	[18]
GABA	Spinal cord	Embryonic	[8,9,18]
	Neural precursors	Embryonic	[10]
	Visual cortex	Embryonic; mature	[11,33]
	Hippocampus	Mature	Gutierrez (2001); [30,32]
	Prefrontal cortex	Mature	[34]
Glutamate	Spinal cord	Embryonic	[18]
	Hippocampus	Mature	Gutierrez (2001); [30,32]
Glycine	Spinal cord	Embryonic	[18]
Dopamine	Sensory ganglion	Embryonic	[12,14,15]
Somatostatin	Hippocampus	Embryonic	[21]
Substance P	Optic tectum	Embryonic; mature	[24]; Tu and Debski (2000)
Norepinephrine	Sympathetic ganglion	Embryonic	[4]

creases under either of these conditions. These investigations of the effects of increases and decreases in electrical activity on neurotransmitter specification are suggestive of homeostatic regulation of excitability, leading to increases and decreases in expression of the inhibitory transmitter GABA.

4. Conclusions

Evidence for homeostatic regulation of transmitter expression both during development and in the mature nervous system, for a range of different transmitters (Table 1), raises the possibility that this process may be a general principle of neuronal development. Several stringent tests of this principle can be envisaged. For transmitters that are excitatory in some tissues and inhibitory in others, depending on transmitter receptor permeability, it will be useful to determine whether electrical activity and Ca^{2+} influx have opposite effects on their expression in different tissues. Coexpression of several transmitters affords the opportunity to determine whether excitatory and inhibitory transmitters are differentially affected by suppression and enhancement of activity. Although the mechanisms by which this form of homeostasis is achieved are still to be determined, this form of plasticity adds another dimension of flexibility to the function of the nervous system.

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