Review

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# Communicating by touch – neurons are not alone

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**Long-distance cell–cell communication is essential for organ development and function. Whereas neurons communicate at long distances by transferring signals at sites of direct contact (i.e., at synapses), it has been presumed that the only way other cell types signal is by dispersing signals through extracellular fluid – indirectly. Recent evidence from *Drosophila* suggests that non-neuronal cells also exchange signaling proteins at sites of direct contact, even when long distances separate the cells. We review here contact-mediated signaling in neurons and discuss how this signaling mechanism is shared by other cell types.**

## Long-distance cell–cell communication

Cells employ many types of signals to coordinate growth and function. Some signals are released systemically and transmit information in the absence of direct cell–cell contact. For example, the hormone insulin distributes throughout the bloodstream, and cells respond similarly regardless if hormone is secreted by the pancreas or is injected intravenously. By contrast, other signals are exposed at the cell surface and convey information while tethered to the plasma membrane. These signals require cell–cell contact. The Notch signaling pathway is an example. Both the Notch receptor and its ligands are transmembrane proteins, and activation of its signal transduction pathway depends on the direct binding of their respective extracellular domains. Nevertheless, one of the enigmas of Notch signaling is that its effects are not limited to neighboring cells but can extend to cells that are more distant (reviewed in [1]). Thus, whereas long-distance signaling is a general property of systemic signals, not all contact-dependent signaling is short-range. In addition, not all contact-dependent signaling is mediated by tethered signals. Neurons extend axons and dendrites that reach long distances over intervening cells and that focus neurotransmitter signaling to specialized contact sites known as synapses. Synaptic signaling requires release of neurotransmitters from the presynaptic cell, travel across the synaptic cleft, and binding to surface receptors (or channels) on the postsynaptic cell (Figure 1) (reviewed in [2]).

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Recent evidence indicates that long-distance, contact-mediated signaling is not unique to neurons, but may be common to many cell types. The existence of cellular projections that extend from non-neuronal cells and that correlate with long-distance signaling has been described in many contexts [3–16]. Recent work directly implicates a particular type of cellular projection called a cytoneme in long-distance signaling [17]. Cytonemes are filopodia that are specialized for signaling [3], and new work shows that *Drosophila* cytonemes synapse with target cells to link communicating cells directly. Moreover, cytoneme synapses are essential for signal uptake and downstream signaling, suggesting a general mechanism for long-distance signaling whereby signals exchange between communicating cells specifically and exclusively at specialized sites of contact. In this review we compare signaling by neurons at axonal and dendritic synapses with signaling by non-neuronal cells at cytoneme synapses, and discuss the conceptual and structural similarities shared by these two types of cell–cell communication.

## Information transfer by neurons

Neurons communicate with target cells by extending cellular processes (dendrites and axons) that make functional synapses, which either capture signals released from synaptic partners or deliver signals to them (reviewed in [2]). The distances that separate the cell body of the neuron and its target cells may be long but, by transporting signals through cell extensions, neurons direct information transfer specifically to the sites of direct cell–cell contact. This mechanism pre-selects signaling partners, ensuring specificity, and allows both signal amplitude and duration to be controlled with exquisite precision.

Neuronal synapses are complex structures in which many cell adhesion proteins, extracellular matrix components, receptors, ion channels, and other proteins involved in signal release and uptake are localized and organized. Although there are many types of neurotransmitters (e.g., small molecules such as acetylcholine and glutamate, ions, neurotrophins, and signaling protein such as Wnt [18,19], transforming growth factor (TGF-β) [20–22], Hedgehog (Hh) [23], epidermal growth factor (EGF) [24], and fibroblast growth factor (FGF) [25]), all neurotransmitters signal by moving from pre- to postsynaptic cells. They are not simply released into extracellular fluid, but are placed specifically in the synaptic cleft, which is a privileged environment. Synaptic partners regulate the properties of the synaptic cleft such that neurotransmitter movement is constrained

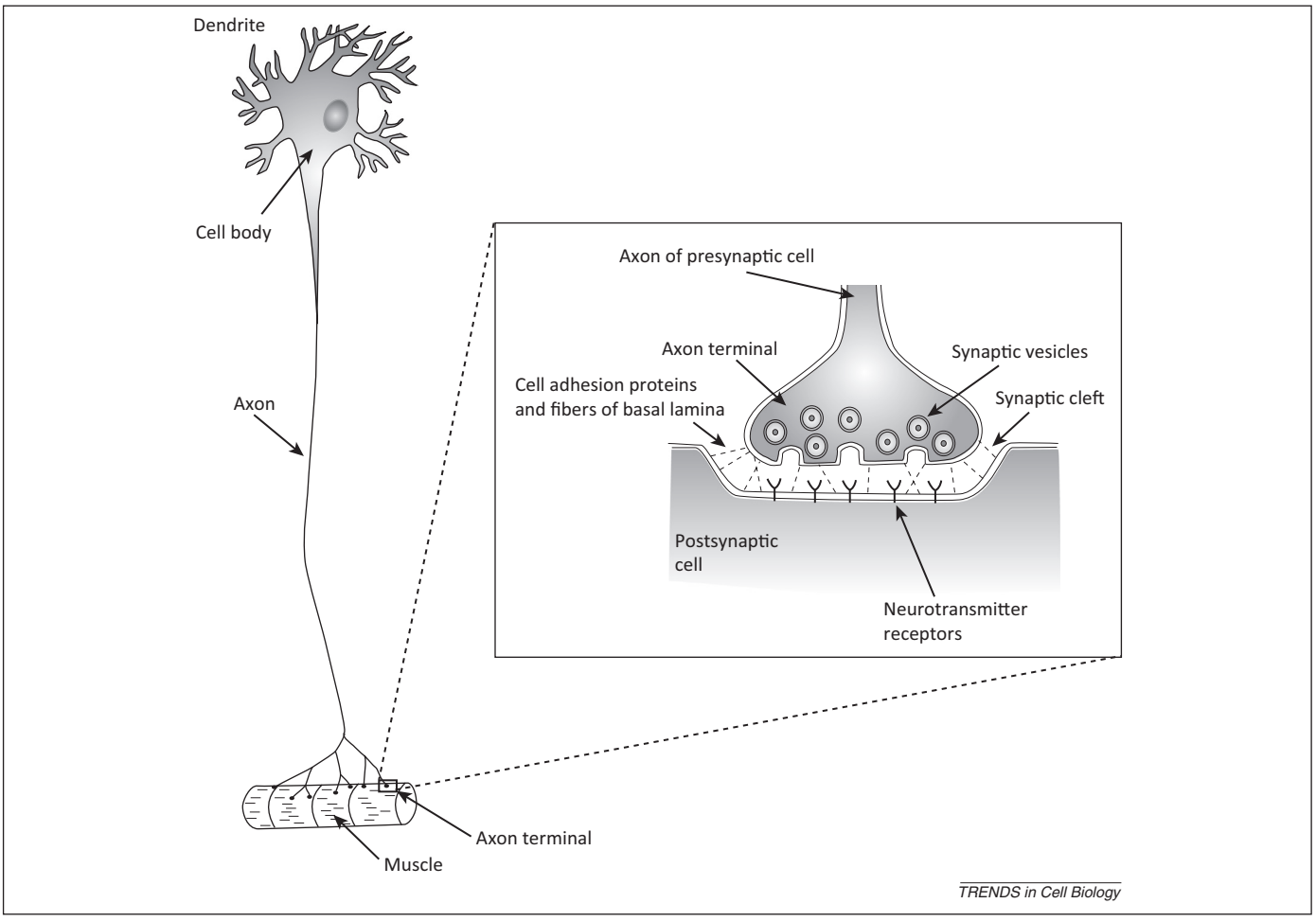


**Figure 1**. Diagram of a neuron that synapses with a muscle cell. The axon that extends from the neuron has specialized terminals that contact the target muscle cell via cell adhesion proteins and basal lamina connections. The synaptic cleft separates the pre- and postsynaptic cells at a defined, set distance, juxtaposing the axon terminal that contains many synaptic vesicles filled with neurotransmitters with the target cell membrane that concentrates neurotransmitter receptors.

and half-life is controlled. Therefore, although neurotransmitters move across the synaptic cleft by diffusion, their dispersion is fundamentally different from that of hormones, whose dissemination is broad and essentially random. At synapses, exchange between a presynaptic cell and a postsynaptic cell is direct and between defined, preselected partners. Specifically, the way information is transferred during this exchange is the key attribute of neuronal signaling that is relevant to this discussion, and not the particulars of neuronal patterning, circuitry, or signal processing, the stability of synapses or the directionality of signaling, the pathfinding process that establishes synaptic contacts or the cell biological mechanisms that generate them, or the process of electrical transmission (reviewed in [2]).

Because neurons focus neurotransmitter release to synapses rather than disperse it either by a general extracellular route or systemically, they do not leave to chance which cells, or even which receptors in a cell, will respond to neurotransmitter. The mechanism that axons employ to transmit the information over long distances (i.e., the propagation of electrical impulses) may be remarkable, and electrical transmission may be a defining feature of neurons, but the key point is that information transfer between distant neurons is juxtacrine at synaptic contacts. This feature conveys information efficiently such that regardless of the distances between the cell bodies of contacting cells, signaling is controlled temporally and spatially (reviewed in [2]).

## Long-distance signaling in non-neuronal tissues

The non-cell autonomous activity of signaling proteins that 'act at a distance' was inferred from the properties of developmental organizers/signaling centers first described over 100 years ago [26–29]. For many years, the 'inducer' molecules responsible for organizer activity were assumed to be small organic molecules that move freely in and out of cells, and that once released from producing cells, diffuse across a developmental field [30]. The discovery that inducers are signaling proteins (morphogens) did not change the general perception that these signals act non-autonomously by diffusing in extracellular fluid after release from producing cells. The fact that signaling proteins have signal peptide sequences has been equated with unregulated release, and the non-autonomous functionality of signaling proteins and their presence at considerable distances from sites of production have been interpreted to support an extracellular route of dispersion. However, the