Information processing by graded-potential transmission through tonically active synapses

Mikko Juusola, Andrew S. French, Raimo O. Uusitalo and Matti Weckström

Many neurons use graded membrane-potential changes, instead of action potentials, to transmit information. Traditional synaptic models feature discontinuous transmitter release by presynaptic action potentials, but this is not true for synapses between graded-potential neurons. In addition to graded and continuous transmitter release, they have multiple active zones, ribbon formations and L-type Ca^{2+} channels. These differences are probably linked to the high rate of vesicle fusion required for continuous transmitter release. Early stages of sensory systems provide some of the best characterized graded-potential neurons, and recent work on these systems suggests that modification of synaptic transmission by adaptation is a powerful feature of graded synapses.

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SENSORY RECEPTOR CELLS, and their postsynaptic interneurons, often respond with graded potentials, have short axons, and a characteristic synaptic topology, to provide dynamic coding of graded presynaptic signals into tonic transmitter release. While action potentials allow information to be reliably transmitted over long distances, graded potentials can only operate over a short distance but allow a higher bandwidth and increase the available information capacity[1–3]. Therefore, early processing of information by graded-potential neurons and synapses can provide significant signal optimization before encoding into action potentials for distance transmission. Recent studies of the fly photoreceptor–interneuron synapse, which uses graded-potentials[4–9], have shown that synaptic transmission changes with mean stimulus intensity, improving information flow. Here we review the major features of this early signal processing, and then illustrate similarities to graded-potential synapses in other sensory systems by comparing their pre- and postsynaptic machinery.

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The presynaptic signal: photoreceptor encoding

Neurons in sensory systems transmit encoded information about the dynamic external environment. Some details of this encoding are now emerging for visual systems. The evidence suggests that for natural surroundings, under natural illumination, photoreceptors code light contrast, which remains unchanged between objects, regardless of the background intensity [contrast (c) is the change in intensity, (ΔI), divided by the mean intensity (I)[4,10,11]; $c = \Delta I/I$; Fig. 1]. Natural images are not random, because their intensity values correlate in space and time. This is easily observed by scanning the surfaces of objects. Although illumination might vary across the scene, the intensity of closely neighboring areas of limited size are very similar. Furthermore, temporal changes in visual input are caused largely by movement of the observer itself. Therefore, it has been proposed that to maximize the information flow to the CNS, a visual system should remove spatial and temporal predictability and redundancies, enhance edges and temporal changes between objects, and encode images of sharpened spatial and temporal contrasts[12].

Photoreceptors might be viewed as adaptive digital–analog converters; they sample discrete events (photon absorptions) and transduce them into graded responses. In dim light, single photons arriving in a photoreceptor of the fly produce brief depolarizations of a few millivolts, called 'quantum bumps'[4,10]. With increasing light intensity, the bumps become smaller, faster and more numerous until they eventually fuse. Because of this adaptational desensitization, full daylight (about 10^7 effective photons s^{-1}) depolarizes invertebrate, and hyperpolarizes vertebrate photoreceptors by less than 30 mV (Refs 10,13). This allows the photoreceptor's entire 30–60 mV operational range to be used to encode light contrasts. In fly photoreceptors a change from dim to full daylight causes about a 10-fold increase in contrast gain, a significant reduction in voltage noise, and therefore an improved signal-to-noise ratio (SNR)[10] (Fig. 1B).

Matching synaptic transmission to the encoded dynamic signal

Although photoreceptor adaptation provides an important initial compression of the natural stimulus range, the stochastic nature of the discrete stimuli, and the large amplification is bound to produce noisy responses. Graded-potential synapses provide the visual system with crucial additional signal processing to cope with this situation and improve the SNR.

When a signal from a graded receptor is transferred to an interneuron through a synapse, noise is added by the quantal release of vesicles. In the absence of action potentials, this noise is added directly to the postsynaptic signal, so that the interneuron response contains both receptor noise and intrinsic synaptic noise[4,8]. If the synapse is to amplify this combined signal while avoiding saturation, it must regulate its

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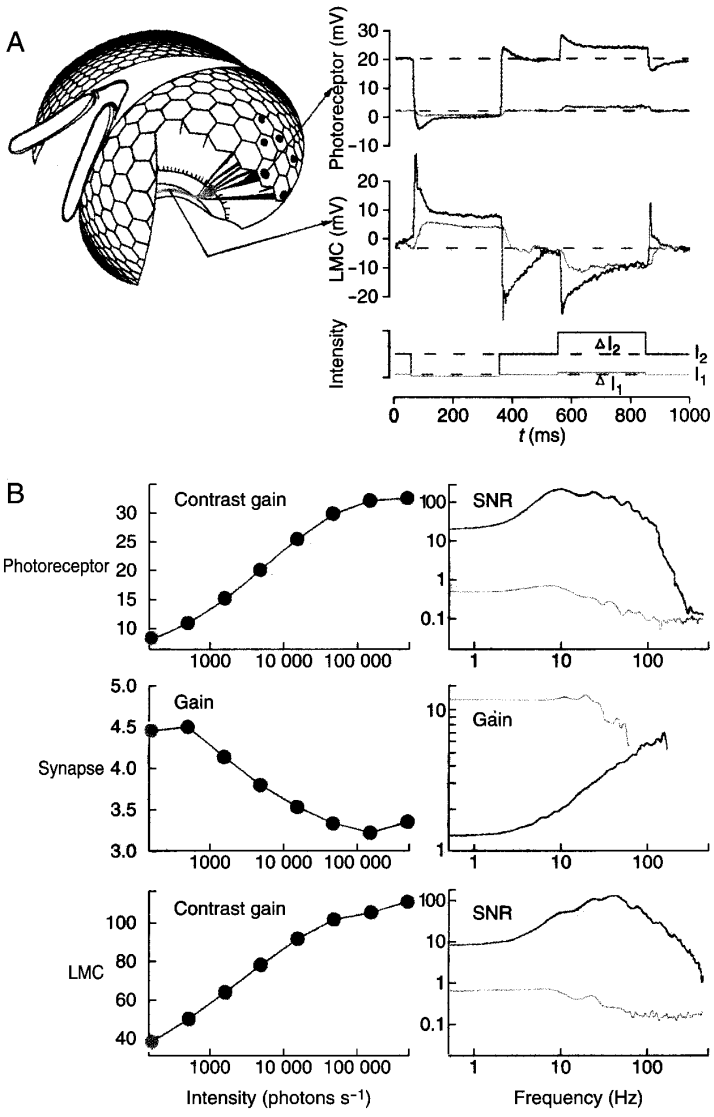

Fig. 1. ***Effects of different light intensities on the photoreceptor–interneuron (LMC) synapse in the blowfly.*** *The synapse between the photoreceptor and the large monopolar cell (LMC) in the compound eye of the blowfly is an example of an adaptive filter, which changes its frequency response with mean intensity. By neural superposition, six R1–R6 photoreceptors (green) from different ommatidia, sample the same point in space. In the lamina (the second layer of visual system) the photoreceptor signals are pooled by separated and structurally identical optic cartridges. Since the number of cartridges matches the number of overlying ommatidia, the signal-to-noise ratio (SNR) is enhanced without degrading visual resolution. Each photoreceptor axon makes over 200 histamine-containing synapses with three first-order interneurons, LMC1–LMC3 (purple). Tonic release of histamine from the synaptic terminals of the photoreceptor axons changes with different light intensities. Binding of histamine to the postsynaptic Cl^- channels modulates the Cl^- conductance and leads to LMC responses.* **(A)** *Step responses and* **(B)** *frequency responses are shown at different mean light intensities (low intensities, red; high intensities, blue). At low intensities, and consequently low SNR, photoreceptor contrast responses (superimposed on a low mean potential, lower dashed line) are low-passed versions of the stimulus, and the slow tonic histamine release dominates LMC responses. Fast depolarizing transient (FDT) channels boost the waveform of the presynaptic signal, and the contrast information can overcome the large synaptic noise. At the synapse, the enhanced signal is low-pass filtered by slow histamine release, which, together with the pooling of photoreceptor signals, conserves low frequencies but removes most uncorrelated high-frequency noise. This increases the reliability of the transmission by conserving low-frequency contrast information. The resulting LMC responses resemble those of low-passed photoreceptors, although amplified and with somewhat improved SNR. At high mean intensities the strategy is different. Increased photoreceptor contrast gain produces large signals with high SNR, and the synaptic low-pass filtering is no longer needed. Even small photoresponses are enhanced by FDT channels, and can modulate the tonic histamine release without being heavily low-pass filtered. Quantal signal transfer at high presynaptic potentials appears to proceed faster with a larger number of samples, and the resulting LMC responses display band-passed characteristics. Temporal transients are enhanced at the expense of steady intensity, reducing redundancy in the image and providing faster information to the CNS. However, the synaptic gain decreases with increasing mean intensity to avoid saturating the operational range of postsynaptic potentials.* Modified from Refs 8–11.

output, in a similar way to a receptor, and it might also need to adjust its frequency response to improve the SNR, taking into account the frequency bands of the noise and the signals of interest to the animal.

Recent work indicates that the photoreceptor–interneuron (large monopolar cell, LMC) synapse in the blowfly is such an adaptive filter, whose frequency response changes with mean intensity[5,7–9] (Fig. 1). Under dim low-SNR conditions, signal reliability is enhanced by spatial and temporal low-pass filtering (Fig. 1A, red lines), which tends to transmit slowly changing signals while rejecting noise. With increasing mean intensity and thus SNR, the synapse becomes more band-pass, now using spatial and temporal antagonism to reduce redundancy and predictability in the stimulus signal (Fig. 1A, blue lines). This adaptive filtering increases the contrast gain of the postsynaptic signal, but decreases the synaptic gain and the transfer delay[8,9] (Fig. 1B). Consequently the synaptic function gives maximum SNR over the frequency range of interest at a given level of illumination. When the SNR is known, it is possible to calculate the capacity of the synaptic information in bits s^{-1} (Refs 3,8). Under bright illumination, photoreceptors transfer >1000 bits s^{-1} and LMCs transfer 1650–2000 bits s^{-1}, far surpassing the capacities of spiking synapses[2,3,8]. This demonstrates the increased efficiency of graded-potential synapses for information transmission.

Adaptive changes in the synaptic frequency response, intrinsic noise and delay, suggest that the increase in mean intensity speeds up the elementary processes of synaptic transmission. This is probably caused by depolarization of the mean presynaptic potential (Fig. 1), which follows the mean input intensity. In the presynaptic terminals, a voltage-sensitive mechanism amplifies and separates small contrast changes from the mean photoreceptor potential[8,14], and the enhanced voltage drives a voltage-sensitive histamine release. The reduction in synaptic gain is due to attenuation at low frequencies[8] causing relatively more signal power at higher frequencies. Some possible mechanisms for this are the generation of low-pass field potentials in the extracellular space[15], presynaptic signal compression by voltage-dependent K^+ channels[8,16], and postsynaptic voltage-sensitive conductances[17,18]. However, non-linear models of the photoreceptor–LMC synapse suggest that serial operations, such as voltage-dependent conductances, are

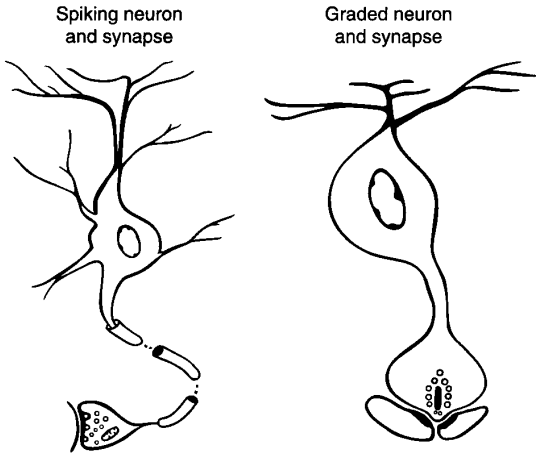

Fig. 2. *Comparison of spiking and graded-potential neurons and synapses.*

more likely to be important than parallel mechanisms, such as extracellular potentials[9].

How do these findings in the visual system of the fly compare to those of other systems that utilize graded potentials and tonic transmitter release? Are there general similarities in structure and function that could provide similar adaptive control of signal processing?

Continuous versus impulsive transmitter release: ribbon and bouton synapses

Current models of synaptic transmitter release include intracellular Ca^{2+}-modulated exocytosis of neurotransmitter from axon terminals. The fundamental process in both spiking and graded synapses seems to be similar. Presynaptic depolarization opens voltage-gated Ca^{2+} channels in the plasma membrane. Ca^{2+} enters the synaptic terminal, diffuses to Ca^{2+} receptor sites, binds to them, and finally triggers vesicular exocytosis, releasing neurotransmitter from small, clear-cored vesicles that are docked at the active zone[19–21]. The rapid timecourse of transmitter release following Ca^{2+} influx suggests that Ca^{2+} acts at a very short distance from the Ca^{2+} channels. In active zones, Ca^{2+} concentration can rise to 100 μM or more within a few hundred microseconds of the channel opening, and then return to submicromolar levels with similar speed[19].

At graded-potential synapses, the presynaptic terminal has to sustain vesicle release at a much higher rate than at impulsive synapses. Measured changes in the membrane capacitance and intracellular Ca^{2+} level in hair cells and vertebrate visual rods suggest a release rate of about 10 000 vesicles s^{-1}, driven by local Ca^{2+} concentrations exceeding 50 μM in the active zones[20,21]. Ca^{2+} channels that inactivate slowly or not at all might facilitate this high local Ca^{2+} concentration, but must be localized and regulated to prevent a significant cellular Ca^{2+} load. In addition, the synaptic machinery must provide for the continuous generation and reuptake of neurotransmitter to meet these demands. Vesicle mobilization in these synapses might also be Ca^{2+} regulated[22]. Some suggested presynaptic controls for Ca^{2+} influx, vesicle production and release include voltage- and Ca^{2+}-activated ion channels, specific synaptic topologies and specific proteins. However, the details of these mechanisms are still largely unknown in both spiking and graded synapses.

Does the morphology of a neuron give some indication of its synaptic function? It appears that there are some helpful markers. While spiking neurons often have elaborately branched processes and long axons that end in synaptic boutons, graded-potential neurons often secrete neurotransmitters from a short unbranched process or from a basal pole (Fig. 2, Table 1). These synapses, which are found in the vertebrate and invertebrate retinas, and in the vertebrate inner ear, typically have many active zones, often with ribbon formations, giving the name of ribbon synapses[23–25]. There are indications that the ribbons are key elements in the accumulation of vesicles and possibly their guidance to release sites. Ribbon synapses are apparently devoid of the synapsins, and some of the other proteins commonly found at spiking synapses that are associated with mobilization of vesicles prior to exocytosis[23–25]

Presynaptic signal processing

The presynaptic Ca^{2+} channels of graded-potential neurons seem to be specialized to deal with graded transmission. Instead of the P- and N-type Ca^{2+} channels found at spiking synapses[26–28], the Ca^{2+} current controlling tonic transmitter release follows L-type channel kinetics in barnacle photoreceptors[29], salamander rods[30], and vertebrate vestibular hair cells[31]. Since these channels have relatively rapid activation

TABLE 1. Comparison of spiking and graded-potential neurons and synapses

Spiking neuron and synapse	Graded neuron and synapse
Long axon, conducting action potentials	Short axon, conducting graded potentials
Pulsed transmitter release	Continuous transmitter release
Bouton terminale with one active zone, but axon might branch to many boutons	Many active zones, ribbon structures
No postsynaptic target cell	Many postsynaptic connections: dyad, triad or tetrad
Presynaptic N- or P-type Ca^{2+} channels	Mainly L-type Ca^{2+} channels
Small clear-cored vesicles	Small clear-cored vesicles
Synapsin present	Devoid of synapsin I
Low gain (1.3–4)	High gain (4–30)
Many transmitters	Transmitters found: glutamate and histamine

The two modes of synaptic transmission are associated with different cellular and synaptic morphologies.

and little or no inactivation, the membrane potential in the terminal exerts a fast, continuous control on the membrane Ca^{2+} conductance. This conductance can also affect the graded signal in the axon terminals, so that opposing voltage- or Ca^{2+}-dependent conductances might be required for reshaping the signal.

Modulation of the Ca^{2+} conductance, and the resulting transmitter release, might be affected by hyperpolarizing and depolarizing signals if the activation range of the presynaptic Ca^{2+} channels has a suitable voltage dependence. Optimally, the mean membrane potential (MMP) should be near the half-activation point (V_{50}) of the channels. The MMP of presynaptic cells in known graded-potential synapses varies from ~–70 mV to ~–20 mV (Fig. 3). Therefore, we might expect to find a comparable variation in the activation range of Ca^{2+} channels. Figure 3A shows the voltage dependence of Ca^{2+} channels in several different vertebrate and invertebrate preparations. In salamander retinal rods and goldfish OFF-bipolar neurons[34,37], the high MMP of about –20 mV can be related to V_{50} values for I_{Ca} of –19 mV and –16 mV, respectively. These activation values for the Ca^{2+} current agree with those of the squid giant synapse, a prototype of spiking synapses[32] shown for comparison by the solid line in Fig. 3A. In contrast, mammalian vestibular hair cells have a low MMP of –50 to –70 mV, and the V_{50} of the Ca^{2+} channels is approx. –33 mV (Ref. 31). In the barnacle photoreceptor–interneuron synapse, which resembles that in the compound eye of the fly and has the same transmitter, histamine[38,39], the very steep activation range of the presynaptic Ca^{2+} current (from –60 to –45 mV) is well matched by the photoreceptor MMP of –60 mV and the normal operating range of –60 to –40 mV (Ref. 29). An exception to this non-inactivating rule of presynaptic Ca^{2+} currents in graded-potential cells is the mouse retinal bipolar cell, which has a T-type current in its terminals[33]. The reasons for this difference are not clear, although one factor might be that the target postsynaptic neurons, amacrine and ganglion cells, have both sustained and spiking behavior.

A variety of conductances are found in presynaptic graded-potential neurons, and these can affect the presynaptic membrane potential. As mentioned above, the presynaptic Ca^{2+} conductance in axons might have positive feedback on its generative depolarization[14], but can be opposed by hyperpolarizing outwardly or inwardly rectifying (usually K^+) conductances that limit the depolarizing and hyperpolarizing shifts, respectively. K^+ channels might also have more subtle effects, such as tuning the membrane frequency response[16,36,40]. K^+ currents that oppose the effects of depolarization have been found in many axon terminals, as well as being abundant in other cell regions. They can be roughly divided into Ca^{2+}-independent (outwardly and inwardly rectifying) currents, and Ca^{2+}-dependent K^+ currents. Voltage-dependent K^+ channels shape the presynaptic signals in vertebrate rods and cones[30] (Fig. 3B), retinal bipolar cells[34], and mammalian vestibular and cochlear hair cells[31,35,41–43] (Fig. 3C). Ca^{2+}-activated K^+ channels are found at the neuromuscular junction[28] and probably numerous other synapses, where they seem to be co-localized with Ca^{2+} channels in the presynaptic membrane[44], so that their activation state can rapidly follow the Ca^{2+} channels. Notably, these channels are also voltage-dependent, and function as outward rectifiers. Ca^{2+}-activated outward currents have been characterized in mammalian hair cells (Fig. 3C),

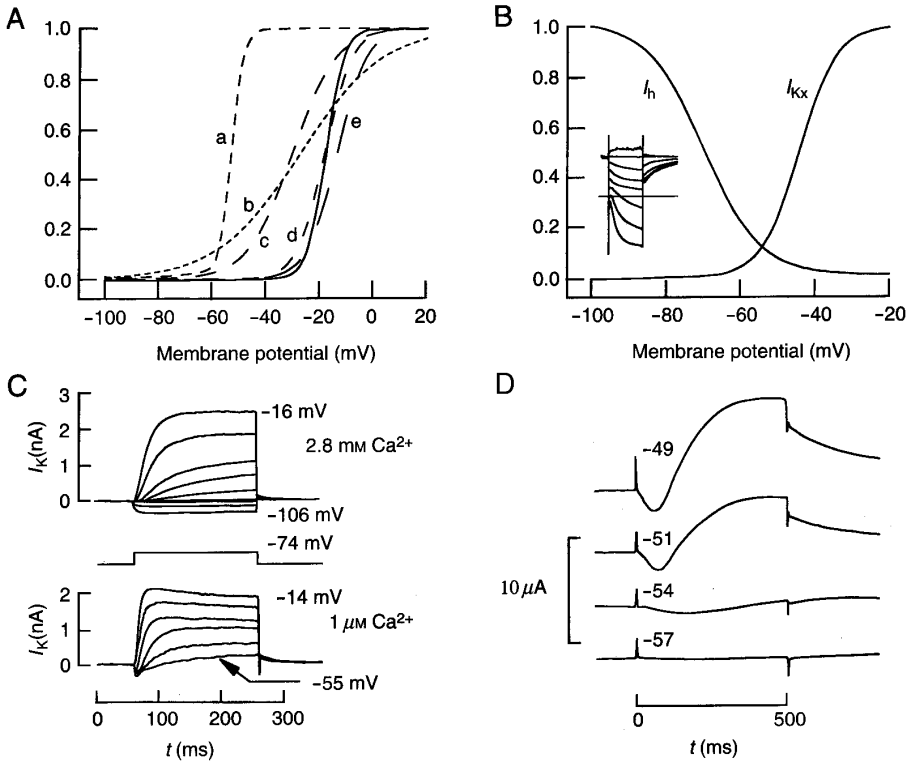

Fig. 3. ***Presynaptic mechanisms shaping the signal transmission in graded-potential synapses.*** **(A)** *Shows activation curves for the Ca^{2+} channels or Ca^{2+} currents in presynaptic terminals. The solid line represents the Ca^{2+} current in the squid giant synapse[32], a typical spiking neuron. The dashed lines show the spread of Ca^{2+} activation in: (a) barnacle photoreceptors[29]; (b) the T-type current in mammalian retinal bipolar neurons[33]; (c) mammalian vestibular hair cells[31]; (d) the L-type current in goldfish retinal OFF-bipolar neurons[34]; and (e) the inner segment of salamander rods[30].* **(B)** *Shows normalized voltage dependence of activation for the outwardly rectifying (I_{Kx}) and inwardly rectifying (I_h) K^+ conductances in vertebrate rod inner segments[30].* **(C)** *Shows families of Ca^{2+}- and voltage-dependent K^+ currents in isolated turtle cochlear hair cells at two different external Ca^{2+} concentrations. These were recorded from patch-clamp experiments in whole cells with steps from a holding potential of –74 mV (Ref. 35). The currents were recorded from a hair cell tuned to low frequency (10 Hz). The current in the condition of a high Ca^{2+} concentration consisted of (in contrast to high-frequency cells) both Ca^{2+}-dependent and Ca^{2+}-independent parts (upper figure), whereas the current in the lower Ca^{2+} concentration consists of only Ca^{2+}-independent part (lower figure). Note that both components act as outward rectifiers from very negative membrane potentials, but could also act as inward rectifiers if the mean membrane potential is more positive, as in insect photoreceptor somata[36].* **(D)** *Shows voltage-clamp currents in terminal 'stumps' of a barnacle photoreceptor in response to 500 ms steps from –60 mV (Ref. 29). Increasing depolarizing voltage steps activated increasing inward (Ca^{2+}) and outward (K^+) currents. The outward current is probably Ca^{2+}-dependent, as in other presynaptic terminals.*

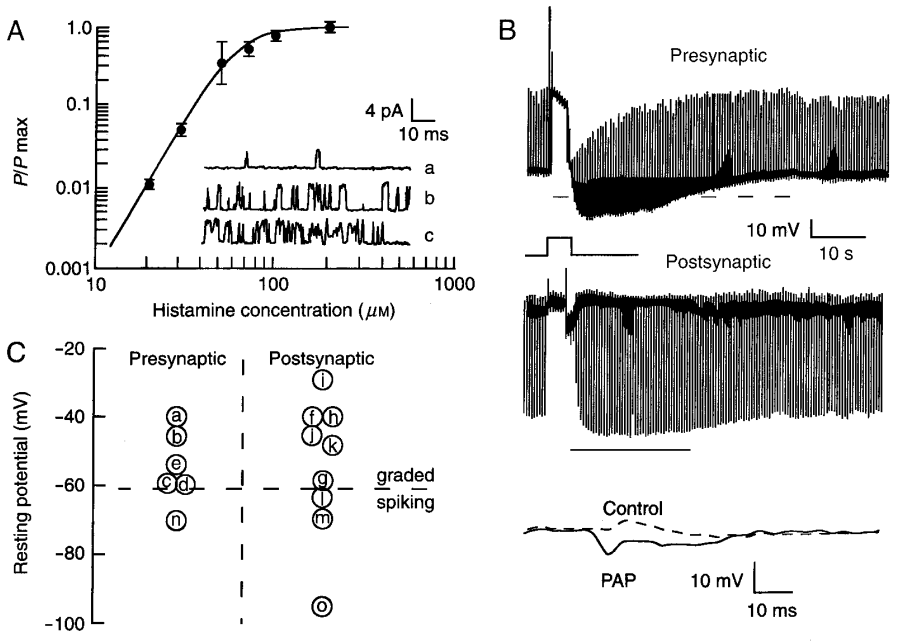

Fig. 4. ***Postsynaptic mechanisms in graded-potential neurons.*** **(A)** *Histamine-gated channels in the postsynaptic (large monopolar cell, LMC) membrane of the photoreceptor–interneuron synapse in the fly illustrate a typical ligand-gated channel in a postsynaptic graded-potential neuron. The dose–response curve shows the normalized open probability (P/P_{max}) as a function of neurotransmitter (histamine) concentration. The curve $P/P_{max} = G^H/(G^H+1)$, where $G=[histamine]/K_d$; [K_d (the apparent dissociation constant) = 60 μM; H (the Hill coefficient) = 4] is very steep. The three traces (a–c) in the insert show single-channel openings from inside-out patches clamped at –70 mV, at concentrations of 30 μM (a), 70 μM (b) and 100 μM (c) histamine[38].* **(B)** *Light-on responses of the presynaptic photoreceptor (upper) and the postsynaptic LMC receptor (middle) to an adapting stimulus (the pulse) and repetitive stimulation with 2 ms flashes are shown. The adapting stimulus depolarizes the photoreceptor and induces an afterhyperpolarization of approx. –20 mV by activating the electrogenic Na^+,K^+ pump[46]. When the mean presynaptic voltage lies below the threshold for transmitter release (dashed line, upper figure) tonic transmitter release is drastically reduced, and the amplitude of the postsynaptic light-on responses is increased (solid line, middle figure). Before the period of increased light-on responses, the reversal potential of the saturated synaptic current was approx. –88 mV (dashed line, bottom traces). During the increased light-on response (solid line) the equilibrium potential shifted below normal by ~10 mV, causing the increased amplitudes of the light-on responses seen above.* **(C)** *Lower mean membrane potentials (–20 to –70 mV) are found in both pre- and postsynaptic graded-potential neurons, compared to those of spiking neurons. The resting potentials of various pre- and postsynaptic neurons are shown; (a) vertebrate hair cell; (b) crab muscle receptor; (c) insect photoreceptor; (d) and (e) crustacean stretch receptor f fibre and s fibre; (f) LMC 1, LMC 2; (g) LMC 3, (h) rod-bipolar; (i) bipolar; (j) horizontal; (k) locust CNS non-spiking interneuron; (l) locust CNS spiking interneuron; (m) motor neuron; (n) squid giant axon; and (o) skeletal muscle.* Adapted from Refs 16,17,47–49.

which also have an inwardly rectifying conductance. Barnacle photoreceptor axons have a similar current[29].

Modification of postsynaptic signals by ligand-gated and voltage-gated channels

It is important for postsynaptic signal processing to retain the presynaptic information capacity. Therefore mean transmitter release should be matched to the affinity, co-operativity and proximity of the postsynaptic receptors, such as ligand-gated ion channels. Graded-potential synapses utilize a variety of such channels and receptors, as well as voltage-gated channels which modulate the changes in membrane potential produced by synaptic transmission, as in presynaptic endings.

Brief channel openings, receptor co-operativity and intracellular reaction cascades can improve the efficiency of signal transmission via ligand-gated conductances[45] (Fig. 4A). In vertebrate retinal neurons, the photoreceptor transmitter glutamate is bound mainly by AMPA or kainate- and metabotropic-receptor subtypes. The AMPA receptor is a ligand-gated channel, with high Ca^{2+} permeability, high co-operativity (Hill coefficient of 1.5), and a mean opening time of 1.3 ms (Ref. 50). The metabotropic receptor does not seem to have a high co-operativity, but the synapse might acquire high gain from an amplification cascade using cGMP and a G protein[51]. In the compound eyes of the blowfly, the histamine-activated Cl^- channels in the LMCs desensitize only slowly if at all[38,52]. There is high co-operativity with three binding sites for the transmitter[52], which makes the dose–response curve steep. Because of the tonic transmitter release, the binding sites are always partially filled and it takes only a small modulation in the mean histamine level to generate large postsynaptic responses, giving a high-gain synapse. Mechanisms like postsynaptic co-operativity and intracellular reaction cascades might be evolutionarily tuned to match the functional demands, as shown by comparative studies in insect photoreceptors[40].

Postsynaptic neurons with graded-potential responses have more-depolarized MMPs than spiking neurons (Fig. 4C). This probably allows a dynamic operational range that can code both negative and positive signals, as with presynaptic elements. Interestingly, some of these neurons are quite small and have to maintain large ion fluxes, demanding effective regulation of their voltage responses. In blowfly LMCs the Cl^- exchanger, which maintains the Cl^- concentration gradient, enables LMCs to change the equilibrium potential of the transmitter-gated conductance quite rapidly in both directions. A change from dark to light adaptation increases transmitter release from the photoreceptor terminals, but reduces the driving force of the postsynaptic Cl^- conductance[53]. The resultant reduction in gain of the ON responses might help to match LMC responses to the contrast properties of their natural environment[54]. On the other hand, after intense stimulation the Cl^- driving force increases and causes increased ON responses[46] (Fig. 4B).

Transmitter release might also be matched to synaptic geometry. The synapses linking rods, bipolar cells and horizontal cells in the mammalian retina have a set of postsynaptic receptors with high affinity located near the periphery of the synaptic cleft. Near the center of the synapse the receptors are of lower affinity[55,56]. This arrangement both maximizes the probability that a released vesicle will cause a postsynaptic response[56] and minimizes the occurrence of false-positive signals.

Concluding remarks

The examples reviewed here show that there are clear differences between the synapses found at the majority of spiking synapses and those between neurons that conduct graded changes in membrane potential. Differences can be seen in both the synaptic morphology and physiology. Graded-potential synapses offer some investigative advantages because the continuous nature of the membrane voltage and current changes are often easier to interpret than complex patterns of action-potential activity. Although few of the molecular mechanisms are known, the qualitative and quantitative characterization of information processing in terms of voltage signals helps us to understand graded-potential synapses and to search for mechanisms. It remains to be seen whether the differences in anatomy and function described here have a more widespread application, but some exceptions are already known. In vertebrate cortical neurons and some smaller neural systems, such as the olfactory bulb, synaptic transmission takes place between dendrites. Here, synapses are sometimes reciprocal, or grouped into glomeruli, as in the cerebellar nuclei. Graded synaptic transmission might be the dominant mode in such dendro–dendritic synapses, even though they have the bouton form[47]. Our expanding knowledge of synapses might resolve these questions, but might also require a more elaborate classification of synaptic functions.

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