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Retinal GABA receptors and visual processing: a model system for presynaptic inhibition

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Introduction

The retina is an ideal system for studying GABA (γ-aminobutyric acid) mediated inhibition in the CNS. Recent work shows that there are a variety of retinal GABA receptors with distinct functional properties, suggesting that these receptors play unique roles in retinal signal processing. Inhibitory signaling is mediated by the ionotropic $GABA_A$ and $GABA_C$ receptors, and the G-protein-coupled $GABA_B$ receptors. The readers are referred to a review by Slaughter (1995) for information on retinal $GABA_B$ receptors. Inhibitory signaling in the vertebrate retina underlies several essential mechanisms of visual information processing, including the center-surround receptive field organization of retinal neurons, and the motion and direction sensitivity of some retinal neurons. Our article will review recent

advances in our understanding of ionotropic GABA receptors, focusing on presynaptic $GABA_C$ receptors, which are highly enriched in the retina. We compare these findings with those in other parts of the CNS to illustrate the common mechanisms used to mediate different types of GABAergic inhibitory signaling.

GABA and the Retina

The retina is a well characterized, layered structure that is ideal for studying GABA-mediated inhibition (Figure 1). The retina can be isolated intact and can be activated by light, its natural stimulus. Responses to these stimuli can be recorded, *in vitro*, from morphologically-identified neurons that are part of well described circuits (Masland, 2001). Using the retina, we can study how GABAergic inhibition contributes to physiologically relevant signaling in an intact CNS circuit. The signaling pathway consisting of photoreceptors, bipolar cells and ganglion cells is the most direct route by which visual information flows to the brain. In the first synaptic layer, the outer plexiform layer (OPL), horizontal cells modulate the transmission between photoreceptors and bipolar cells (Figure 1). In the second synaptic layer, the inner plexiform layer (IPL), amacrine cells modulate transmission between bipolar cells and ganglion cells (Figure 1). GABA mediated signaling occurs in both synaptic layers.

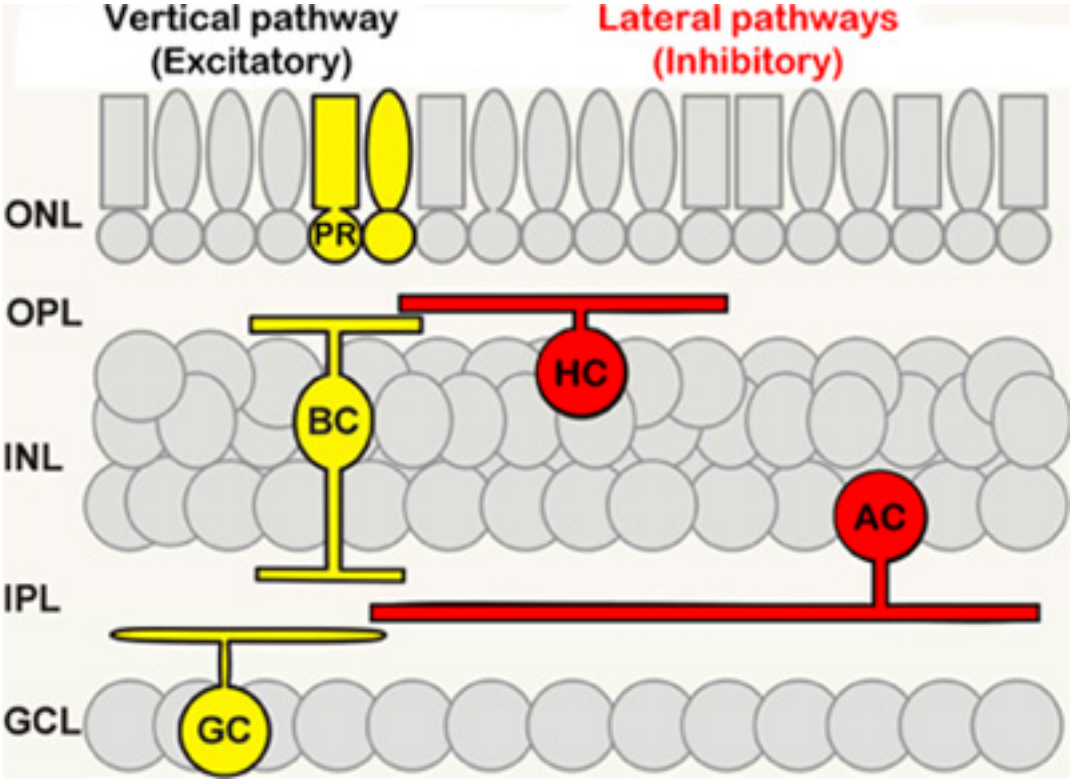

Figure 1. The retina is a well-organized, laminar structure composed of five distinct classes of neurons. Photoreceptors (PR) are activated by light and synapse onto bipolar cells (BC) and horizontal cells (HC) in the outer plexiform layer (OPL). Bipolar cells then synapse onto ganglion cells (GC) and amacrine cells (AC) in the inner plexiform layer (IPL). The vertical, excitatory pathway (yellow) consisting of photoreceptors, bipolar cells and ganglion cells is modulated by two lateral, inhibitory pathways (red). These inhibitory signaling pathways are mediated by horizontal cells (HC) in the outer retina and amacrine cells (AC) in the inner retina.

GABA receptor diversity in the retina

The retina is perhaps the best place in the CNS to study the roles of $GABA_A$ and $GABA_C$ receptors because both classes are found in abundance. These two classes of ionotropic GABA receptors share some similarities; they both are composed of five subunits and gate chloride channels. However, $GABA_A$ and $GABA_C$ receptors are molecularly distinct and possess different functional properties. $GABA_A$ receptors are heteromeric complexes, comprised of different

combinations of the following subunits, α, β, γ, δ and π. Expression studies suggest that only limited subunit combinations form functional receptors in the CNS (Mehta & Ticku, 1999). $GABA_C$ receptors, by contrast, are most likely comprised of heteromeric combinations of ρ1 and ρ2 subunits (Enz *et al*., 1995; Zhang *et al*., 1995; Yeh *et al*., 1996). Recent findings suggest that ρ1 subunits are required for the expression of $GABA_C$ receptors *in vivo* (McCall *et al*., 2002) .

While studies of both recombinant and retinal $GABA_C$ receptors indicate that they possess ρ subunits (Amin & Weiss, 1994; Enz *et al*., 1995), the subunit composition of native $GABA_C$ receptors remains unknown. Given that both $GABA_A$ and $GABA_C$ receptor subunits are present on bipolar cells, do these subunits coassemble to form $GABA_C$ receptors? Most evidence suggests that ρ subunits do not coassemble with $GABA_A$ receptor subunits. Shimada *et al*. (1992) failed to find any evidence that ρ1 subunits were coassembled with α, β, or γ2 $GABA_A$ receptor subunits. In addition, co-immunoprecipitation assays failed to show evidence for coassembly of ρ1 subunits and α and β subunits (Hackam *et al*., 1998). On the other hand, several studies suggest that heterologously expressed ρ and γ2 $GABA_A$ receptor subunits form receptors with properties similar to native $GABA_C$ receptors (Qian & Ripps, 1999; Pan *et al*., 2000; Qian & Pan, 2002), but these expressed receptors differed from native receptors since they were potentiated by barbiturates. Immunolabelling studies in retina (Koulen *et al*., 1998; Haverkamp & Wässle, 2000) found no evidence for colocalization of $GABA_A$ receptor subunits with ρ subunits, suggesting that these subunits did not combine to form $GABA_C$ receptors in the retina.

Physiological properties of $GABA_A$ and $GABA_C$ receptors

Although $GABA_A$ and $GABA_C$ receptors both gate chloride channels, these two classes of receptors have distinct biophysical characteristics

that confer unique functional properties. $GABA_C$ receptors are about ten-fold more sensitive to GABA than the most common types of $GABA_A$ receptors (Feigenspan & Bormann, 1994). In addition, $GABA_C$ receptors open and close more slowly than the typical $GABA_A$ receptor and mediate prolonged current responses (Amin & Weiss, 1994; Qian & Dowling, 1995; Chang & Weiss, 1999). Using recombinant ρ1 $GABA_C$ receptors, Chang and Weiss (1999) attributed the slow current onset to the slow association rate of GABA to a restricted access binding site. The slow decay of the current response mediated by the recombinant $GABA_C$ receptors was attributed to the open receptor pore hindering agonist unbinding. The slow native $GABA_C$ receptor-mediated response component in rod bipolar cells was eliminated in ρ1 subunit knockout mice (McCall *et al*., 2002, Figure 2). The briefer GABA responses in knockout mice were mediated by the remaining $GABA_A$ receptors. Thus compared to conventional $GABA_A$ receptors, $GABA_C$ receptors are activated by lower concentrations of GABA and mediate more prolonged inhibitory signals. $GABA_A$ and $GABA_C$ receptors also display unique pharmacological signatures. $GABA_C$ receptors, unlike $GABA_A$ receptors, are neither antagonized by bicuculline nor potentiated by barbiturates or benzodiazepines. Conversely, $GABA_C$ receptors, but not $GABA_A$ receptors are antagonized by TPMPA ((1,2,5,6-Tetrahydropyridin-4-yl) methylphosphinic acid).

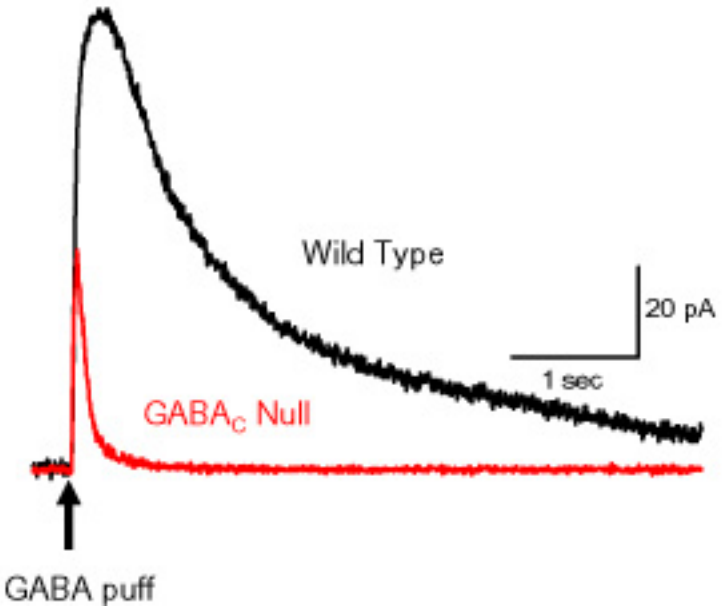

Figure 2. Retinal GABAC receptors mediate prolonged GABA responses in rod bipolar cells. Shown are GABA currents in response to focal, puff applications of GABA (100 µM) to the axon terminals of rod bipolar cells in retinas from WT and GABACR null mice. Responses from WT mice are long lasting and are mediated mainly by GABAC receptors, and to a lesser extent, by GABAA receptors. Responses from mice that lack GABAC receptors are much briefer and are mediated exclusively by GABAA receptors. Reprinted with permission in modified form from McCall et al, 2002, *Journal of Neuroscience*. © 2002 by the Society for Neuroscience.

Retinal locations of GABAC and GABAA receptors

A diversity of GABAA receptors is found in the retina. GABAA receptors are found on all types of retinal neurons and they mediate both pre- and postsynaptic inhibition. Because GABAA receptors are located in both the IPL and OPL, they can, in principle, modulate signaling between photoreceptors and bipolar cells, as well as signaling between bipolar and ganglion cells. *In situ* hybridization and immunocytochemical studies suggest there are a variety of GABAA receptors in the retina arising from different subunit combinations (Greferath *et al*., 1995; Wassle *et al*., 1998; Zhang *et al*., 2003). In

addition to distinct distributions of $GABA_A$ receptor subunits on different retinal interneurons, there are also different assortments of $GABA_A$ receptor subunits on a single neuron (Wassle *et al*., 1998), suggesting that there are distinct $GABA_A$ receptors on individual retinal neurons. Based on functional studies of heterologously expressed $GABA_A$ receptor subunits (reviewed by Mehta & Ticku, 1999) these findings suggest that retinal $GABA_A$ receptors may have unique signaling roles. Although these studies strongly suggest a variety of $GABA_A$ receptor-mediated functions in the retina, it is not known whether they have distinct roles because subunit-specific physiological and pharmacological studies have not been performed. The determination of their functional roles must await the development of subunit-specific pharmacological agents.

The distribution of $GABA_C$ receptors in the retina is more limited than $GABA_A$ receptors. $GABA_C$ receptors only mediate presynaptic inhibition. Immunohistochemical studies demonstrate that $GABA_C$ receptors are most abundant in the IPL, specifically on bipolar cell terminals, at contacts made by amacrine cells (Enz *et al*., 1996; Koulen *et al*., 1997; Fletcher *et al*., 1998). By contrast, immunolabeling in the OPL is generally weaker and more diffuse (Haverkamp *et al*., 2000). Although some studies have shown that $GABA_C$ receptors are also present on cone photoreceptor terminals in pig and mouse retina (Picaud *et al*., 1998; Pattnaik *et al*., 2000), where they might play a role in modulating glutamate release, electrophysiological studies suggest that GABA does not play a major role in controlling glutamate release from cone photoreceptors (Verweij *et al*., 1996; Kamermans *et al*., 2001). Work by Kamermans and colleagues (2002) suggests that GABA may be involved in slow modulation of this synapse and does not act as a traditional, fast inhibitory transmitter.

The anatomical evidence for $GABA_C$ receptor localization is confirmed by electrophysiological recordings from bipolar cells

showing that the largest $GABA_C$ receptor-mediated responses are at the bipolar cell terminals (Lukasiewicz *et al*., 1994; Matthews *et al*., 1994; Wu & Maple, 1998; Shields *et al*., 2000). GABA responses in mammalian rod bipolar cells are relatively insensitive to blockade by bicuculline, indicating that they are mediated primarily by $GABA_C$ receptors (Euler & Wässle, 1998; Shields *et al*., 2000; McCall *et al*., 2002). Electrophysiological studies also indicate that a type of horizontal cell in some species of fish has $GABA_C$ receptors (Qian & Dowling, 1993; Dong *et al*., 1994). In most vertebrates, however, horizontal cells do not express $GABA_C$ receptors (Stockton & Slaughter, 1991; Blanco *et al*., 1996; Koulen *et al*., 1997). Because subunit specific antibodies do not exist for different $GABA_C$ ρ subunits, and as there are no pharmacological agents available that are specific for individual ρ subunits, our ability to study different subtypes of $GABA_C$ receptors is limited. As the majority of the $GABA_C$ and $GABA_A$ receptors are present in the inner retina, where the function of GABAergic synaptic transmission has been most extensively studied, we will focus our further discussion of the function roles of GABA receptors on IPL information processing.

GABA-mediated inhibition and IPL information processing

Amacrine cells mediate lateral and feedback inhibitory signaling in the inner plexiform layer. Amacrine cells comprise the most diverse class of retinal interneurons (MacNeil & Masland, 1998). Approximately one half of all amacrine cells are GABAergic and this population is composed of morphologically diverse subtypes (Pourcho & Goebel, 1983) that serve different functions, as described below. Amacrine cells synapse onto bipolar cell terminals, ganglion cell and amacrine cell dendrites, which are all located in the IPL. Reciprocal synapses occur between amacrine cell processes and bipolar cell terminals that modulate bipolar cell output (Dowling & Boycott, 1966). Amacrine cells are activated by bipolar cell glutamate release and, in turn,

release GABA back onto the bipolar cell terminal. Lateral amacrine cell processes also make synaptic contacts onto bipolar cell terminals and ganglion cell dendrites and mediate lateral inhibition, as described below.

GABA receptor modulation of bipolar cell output

The predominant role of $GABA_C$ receptors in the retina is to mediate presynaptic inhibition of the bipolar cell output (Lukasiewicz *et al*., 2004). $GABA_C$ receptors mediate a significant fraction of GABA-evoked responses at bipolar cell terminals (Lukasiewicz *et al*., 1994; Matthews *et al*., 1994; Pan & Lipton, 1995), which, as stated above, are characterized by slow activation and deactivation kinetics and by high GABA sensitivity. Synaptic activation of these receptors by light (Eggers & Lukasiewicz, 2006) or other stimuli (Hartveit, 1997; Lukasiewicz & Shields, 1998; Shen & Slaughter, 2001) confirms that $GABA_C$ receptors mediate a significant fraction of presynaptic inhibition at bipolar cell terminals, although $GABA_A$ receptors also supply presynaptic inhibition to bipolar cells. GABA receptors on bipolar cell axon terminals play a number of roles in visual processing. $GABA_C$ receptors have been shown to control the excitatory output of bipolar cells onto ganglion cells (Lukasiewicz & Werblin, 1994; Dong & Werblin, 1998) and amacrine cells (Bloomfield & Xin, 2000; Matsui *et al*., 2001).

Presynaptic $GABA_C$ receptor-mediated inhibition can shape the temporal properties of the glutamate signal from bipolar cell to ganglion cells. Dong & Werblin (1998) suggest that $GABA_C$ receptor-mediated inhibitory feedback gives rise, in part, to transient responses in ganglion cells, although this may not be the primary mechanism of transient response formation (Bieda & Copenhagen, 2000). Freed *et al* (2003) reported that the blockade of $GABA_C$ receptors decreased the correlated bursting of spontaneous excitatory postsynaptic currents (EPSCs) and spikes in ganglion cells and amacrine cells, suggesting a

temporal processing role for $GABA_C$ receptors.

$GABA_C$ receptor-mediated inhibition contributes to the center-surround receptive field organization of ganglion cells. Illumination of the receptive field center depolarizes ON center ganglion cells and hyperpolarizes OFF center ganglion cells (Werblin & Dowling, 1969). Receptive field surround illumination antagonizes the response to center illumination, hyperpolarizing ON center ganglion cells and depolarizing OFF center ganglion cells. The classical center-surround receptive field organization of ganglion cells reflects spatial signal processing and is usually attributed to lateral interactions between horizontal cells and photoreceptors at the OPL (Baylor *et al*., 1971). However, work by Cook & McReynolds (1998) demonstrated that lateral interactions between amacrine cells and bipolar cells and ganglion cells at the IPL accounts for a significant amount of ganglion cell surround inhibition. A large component of this surround input is mediated by $GABA_C$ receptors (Bloomfield & Xin, 2000; Flores-Herr *et al*., 2001; Ichinose & Lukasiewicz, 2005), indicating that lateral inhibitory signals from amacrine cells to bipolar cells mediate a portion of the ganglion cell surround. This is illustrated in Figure 3, which shows that inhibition of ganglion cells, mediated by a dim surround illumination, is blocked by $GABA_C$ receptor antagonists (Ichinose & Lukasiewicz, 2005). Postsynaptic $GABA_A$ receptors on ganglion cells and amacrine cells also mediate a component of the surround input measured in amacrine (Bloomfield & Xin, 2000) and ganglion cells (Cook & McReynolds, 1998; Flores-Herr *et al*., 2001; Ichinose & Lukasiewicz, 2005).

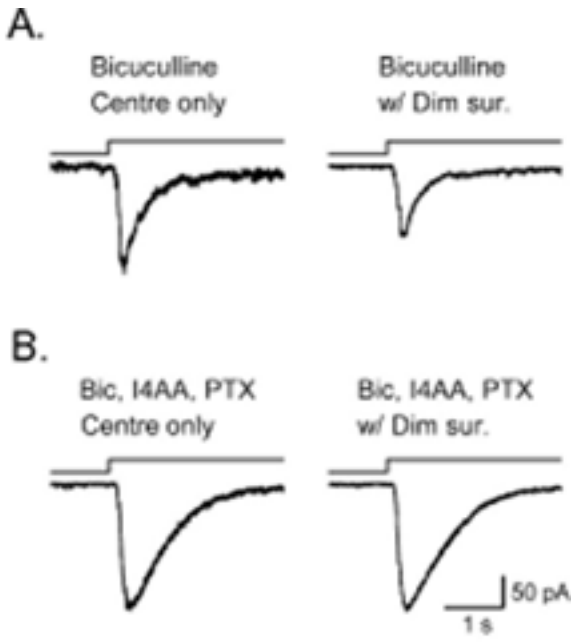

Figure 3. Lateral inhibition mediated by GABA$_C$ receptors located in the IPL contributes to the inhibitory, receptive field surround of ganglion cells. A. Dim surround illumination decreases the response of ganglion cells to a spot of light. Surround inhibition occurred in the presence of the GABA$_A$ receptor blocker bicuculline, indicating that it was mediated by GABA$_C$ receptors. B. Dim surround inhibition was eliminated when GABA$_C$ receptors are blocked with the addition of picrotoxin and I4AA (imidazole-4-acetic acid), non-specific GABA receptor antagonists. Reprinted with permission in modified form from Ichinose and Lukasiewicz, 2005, *Journal of Physiology*. © 2005, The Physiological Society.

Temporal tuning of inhibition by GABA receptors

GABA$_A$ receptors are often found with GABA$_C$ receptors on bipolar cell terminals, but the relative numbers of these two classes of receptor vary with bipolar cell type (Euler & Wässle, 1998; Shields *et al*., 2000). Because bipolar cell GABA$_A$ and GABA$_C$ receptors have different kinetic properties, the time course of GABA currents in different bipolar cell types depends on the relative proportions of GABA$_A$ and GABA$_C$ receptors. Rod bipolar cells, which possess predominantly GABA$_C$ receptors, had long-lasting responses, whereas OFF cone bipolar cells, which had a larger fraction of GABA$_A$

receptors, had significantly briefer responses, as illustrated in Figure 4 (Shields *et al*., 2000). The temporal characteristics of inhibition may be matched to the temporal characteristics of excitation in rod and cone bipolar cells. Rod mediated responses are slower than cone mediated responses, attributable to longer synaptic transfer times at rod synapses than at cone synapses (Schnapf & Copenhagen, 1982). Also, cone-mediated synaptic events in ON cone bipolar cells are longer than those in OFF cone bipolar cells (Ashmore & Copenhagen, 1980), attributable to the presence of metabotropic glutamate receptors on ON cone bipolar cell dendrites (Slaughter & Miller, 1981; Nawy & Jahr, 1990) and AMPA and/or kainate receptors on OFF cone bipolar cell dendrites (DeVries, 2000). GABAergic inhibition at the bipolar cell terminals appears to be matched to the kinetics of the excitatory responses; rod bipolar cells have the slowest excitatory responses and the largest complement of $GABA_C$ receptors, whereas OFF cone bipolar cells have the fastest excitatory responses and possess a larger complement of $GABA_A$ receptors.

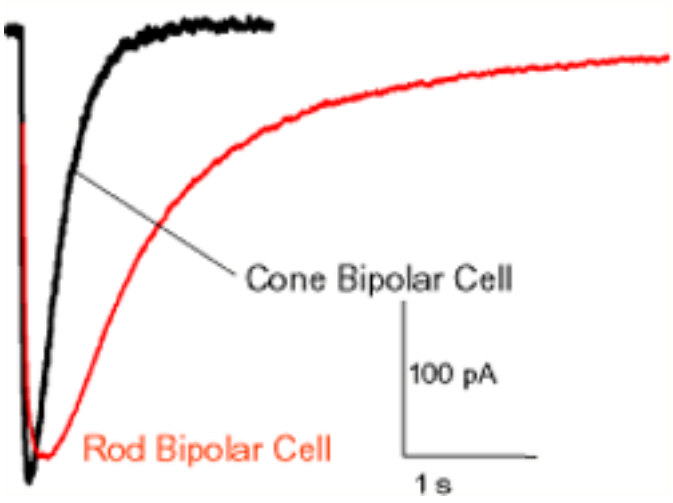

Figure 4. $GABA_A$ and $GABA_C$ receptors temporally tune GABA responses to different bipolar cell types in the retina. Current responses to puff applications of GABA (200 µM), applied to the axon terminals of bipolar cells in slices from ferret retinas (GABA currents were inward because E_{Cl} for these experiments was -2 mV and bipolar cells were voltage clamped to -70 mV). Current responses in rod bipolar cells (red trace) were prolonged and mediated largely by $GABA_C$ receptors. By contrast, current

responses from OFF cone bipolar cells (black trace) were briefer and mediated by a larger fraction of GABA$_A$ receptors. Reprinted with permission in modified form from Shields et al, 2000, *Journal of Neuroscience*. © 2000 by the Society for Neuroscience.

While GABA receptor kinetics may shape synaptic responses, it is not known how significant this role is because the time course of inhibition is attributed to both receptor kinetics and the time course of GABA release. Recent work addresses this issue and shows that GABA$_A$ and GABA$_C$ receptor properties are important factors in determining the timecourse of light-evoked inhibitory postsynaptic currents (IPSCs) in rod bipolar cells (Eggers & Lukasiewicz, 2006). Elimination of slowly responding GABA$_C$ receptors shortened the time course of light-evoked IPSCs, confirming that receptor properties affect light-evoked IPSC time course (Figure 5, Lukasiewicz *et al*., 2004). These findings suggest that light-evoked synaptic inputs to rod bipolar cells are temporally tuned by postsynaptic GABA receptor properties.

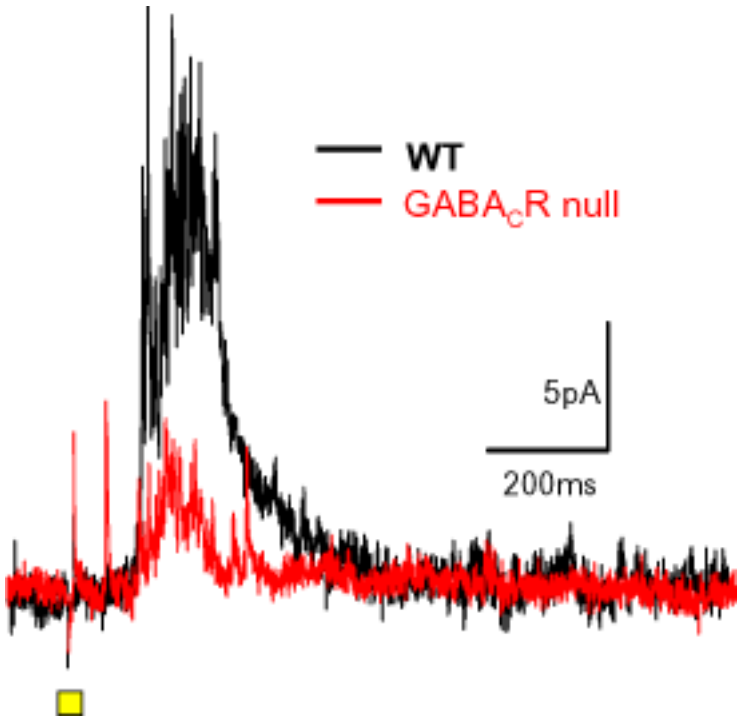

Figure 5. GABA$_C$ receptors prolong light-evoked, synaptic inhibition in rod bipolar cells. Brief light flashes (10 ms, indicated by yellow bar below

response traces) were used to evoke inhibitory currents in rod bipolar cells from WT and GABA$_C$R null mice. Light-evoked inhibition recorded in WT mice was larger and more prolonged (black trace) compared to inhibition recorded from mice that lacked GABA$_C$ receptors (red trace).

GABA$_C$ receptors may mediate spillover transmission

GABA$_C$ receptors have a higher affinity for GABA than GABA$_A$ receptors and thus are more likely to be activated by spillover transmission from neighboring synapses. When GABA uptake was blocked in the retina, GABA$_C$, but not GABA$_A$ receptor-mediated synaptic responses were enhanced (Ichinose & Lukasiewicz, 2002, Figure 6), demonstrating that GABA$_C$ receptors were more sensitive to spillover transmission. When GABA uptake was reduced, the enhanced GABA$_C$ receptor-mediated inhibition reduced ganglion cell sensitivity to illumination (Ichinose & Lukasiewicz, 2002), similar to the reductions in ganglion cell light sensitivity produced by surround illumination (Sakmann & Creutzfeldt, 1969; Thibos & Werblin, 1978). These results suggest that GABA transporters limit the extent of light-evoked inhibitory transmission at the inner retina by restricting spillover activation of GABA$_C$ receptors. An alternative explanation to enhanced spillover upon uptake blockade is suggested by the findings of Chang and Weiss (1999), demonstrating that the binding site of recombinant GABA$_C$ receptors may have more restricted access than the binding site on GABA$_A$ receptors. In this scheme, GABA$_C$ receptors may be synaptically localized and the blockade of GABA uptake enhances GABA$_C$ receptor-mediated responses by increasing the concentration of GABA in the synapse, countering the restricted binding site access.

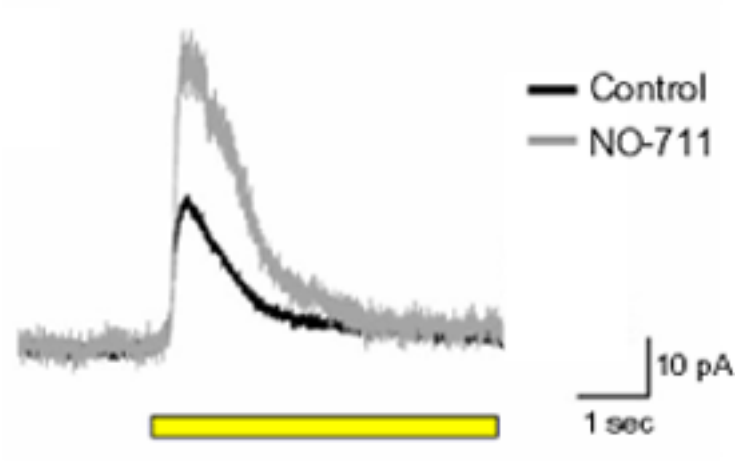

Figure 6. Blockade of GABA uptake increases spillover transmission and enhances GABAc receptor-mediated responses. Light-evoked, inhibitory synaptic currents (black trace) recorded from bipolar cells in salamander retina (duration of light stimulation indicated by yellow bar below responses). Light-evoked inhibitory currents were potentiated (grey trace) after GABA uptake was blocked with NO-711. This potentiation did not dependent on $GABA_A$ receptors because is still occurred in the presence of bicuculline. Reprinted with permission in modified form from Ichinose and Lukasiewicz, 2002, *Journal of Neuroscience*. © 2002 by the Society for Neuroscience.

GABA receptors in other parts of the CNS play similar roles to those in the retina

Presynaptic inhibition modulates neurotransmission in many areas of the CNS

In other parts of the CNS, GABA receptors play similar roles to those described above in the retina. The presynaptic modulation of neurotransmitter release by ionotropic GABA receptors is one parallel. $GABA_A$ receptors, present on GABAergic neuron terminals in the suprachiasmatic nucleus (Belenky *et al*., 2003) and in the hippocampus (Axmacher & Draguhn, 2004) decrease GABA release. In the adult spinal cord, presynaptic $GABA_A$ receptors depolarize glycinergic terminals, due to a relatively positive E_{Cl} in the axon terminal, and decrease action potential-mediated release, most likely

due to inactivation of voltage-gated Ca^{2+} or Na^{+} channels (Jang *et al*., 2002). $GABA_A$ receptors are also presynaptically located on the terminals of cerebellar interneurons. Early in development, when E_{Cl} is more positive than the resting potential, GABA released from these interneurons feedbacks onto $GABA_A$ autoreceptors (Mejia-Gervacio & Marty, 2005) to further enhance GABA release (Figure 7). In a similar manner, presynaptic $GABA_A$ receptors on the Calyx of Held increase glutamate release in early development and this positive feedback function is taken over by glycine later in development (Turecek & Trussell, 2002).

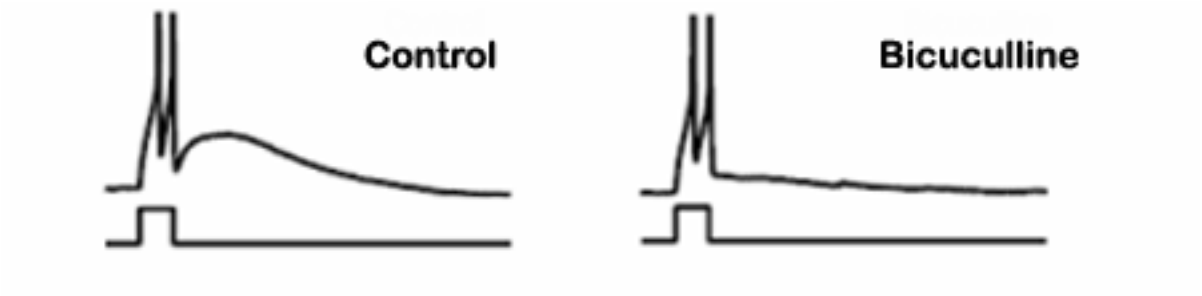

Figure 7. $GABA_A$ receptors on molecular layer neurons in the cerebellum mediate an afterdepolarization. $GABA_A$ autoreceptors are activated by GABA release, and this GABA feedback signal causes an afterdepolarization after spiking. This afterdepolarization is mediated by $GABA_A$ receptors because it can be blocked by bicuculline. Reprinted with permission in modified form from Mejia-Gervacio & Marty, 2005, *Journal of Physiology*. © 2005, The Physiological Society.

While $GABA_C$ receptors are primarily expressed in the retina, they are also expressed in the superior colliculus, on GABAergic terminals (Boller & Schmidt, 2003). Although $GABA_C$ receptors in the superior colliculus neurons are not as extensively studied as in the retina, they have been shown to decrease the paired-pulse depression of GABAergic IPSCs, consistent with their roles as autoreceptors (Kirischuk *et al*., 2003, Figure 8). While presynaptic ionotropic GABA receptors exist outside the retina, in many cases they function as autoreceptors, modulating GABA release. By contrast, presynaptic

GABA receptors on retinal bipolar cells are innervated by GABAergic amacrine interneurons, which limit glutamate release, resulting in the modulation of the transmission of visual information.

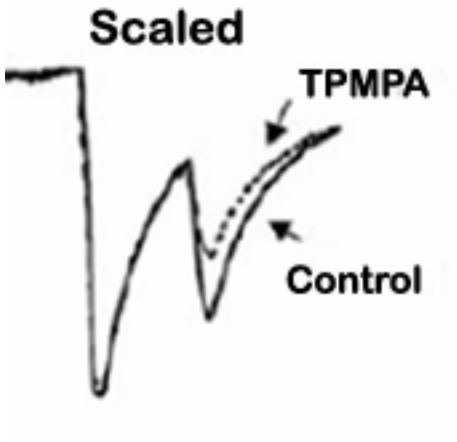

Figure 8. Presynaptic GABA$_C$ receptors decrease synaptic depression in the superior colliculus. The amplitude of the second IPSC evoked by a pair of stimuli is reduced, indicating that paired pulse depression occurred at this synapse. Paired pulse depression increased (dotted trace) after GABA$_C$ receptors were blocked by the addition of the GABA$_C$ receptor antagonist TPMPA. These data suggest that GABA$_C$ receptors normally limit paired pulse depression. Reprinted with permission in modified form from Kirischuk et al, 2003 *European Journal of Neuroscience*, © 2003, Federation of European Neuroscience Societies.

GABA$_A$ receptors can also mediate tonic inhibition

GABA release in the retina is mediated by graded potential release as well as TTX-sensitive spiking mechanisms (Cook & McReynolds, 1998; Shields & Lukasiewicz, 2003). In other parts of the central nervous system, at low spiking frequencies, GABA is most often released in spike-dependent fashion, giving rise to pulsatile, synchronous release (Lu & Trussell, 2000). By contrast, interneurons in the hippocampus show prolonged, asynchronous GABA release (Hefft & Jonas, 2005), producing more extended activation of GABA$_A$ receptors that yields sustained inhibition. Further evidence for GABA$_A$

receptor-mediated tonic inhibition is put forth by Mitchell and Silver (2003), who found that tonic, shunting $GABA_A$ receptor-mediated inhibition of cerebellar granule cells reduced excitation and altered the excitatory transmission input-output relationship.

Spillover and tonic neurotransmission are usually associated with the activation of high affinity receptors, such as retinal $GABA_C$ receptors, that are activated by much lower concentrations of GABA than are present at the synapse (Ichinose & Lukasiewicz, 2002). In other parts of the nervous system, comparable spillover and tonic inhibitory transmission is mediated by different subtypes of $GABA_A$ receptors. Similar to $GABA_C$ receptors, δ and α6/α4 containing $GABA_A$ receptors desensitize slowly and have a higher affinity for GABA than the more typical α1βγ $GABA_A$ receptors (Saxena & Macdonald, 1996; Brown *et al*., 2002). In cerebellar granule (Nusser *et al*., 1998) and dentate gyrus cells (Nusser & Mody, 2002; Wei *et al*., 2003) δ and α6 (cerebellum) or α4 (dentate gyrus) containing $GABA_A$ receptors are located extrasynaptically. These $GABA_A$ receptors are activated by spillover (Wei *et al*., 2003) in the dentate gyrus and mediate tonic $GABA_A$ currents in cerebellar granule cells (Brickley *et al*., 1996; Brickley *et al*., 2001). Brickley *et al*. (2001) demonstrated that extrasynaptic $GABA_A$ receptors in the cerebellum contain an α6 subunit by knocking out the α6 subunit. This eliminated only the extrasynaptic receptors, as the α6 knockout mice showed no tonic currents, but synaptic currents were unchanged (Figure 9).

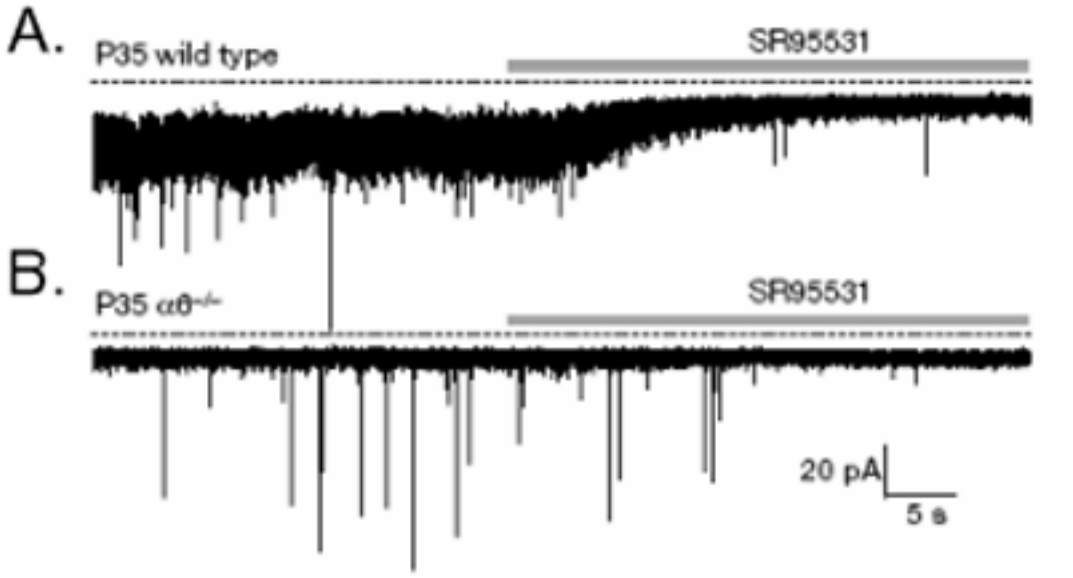

Figure 9. Tonic, but not phasic, GABA receptor-mediated currents in cerebellar granule cells are decreased when the α6 GABA$_A$ receptor subunit is knocked out. A. In WT mice, both phasic and tonic GABA$_A$ receptor-mediated currents are blocked by the application of SR95531. B. In mice that lack α6δ GABA$_A$ receptor subunits, the tonic current was eliminated, but the phasic current remained unchanged. These data indicate that tonic currents were mediated by α6δ-containing GABA$_A$ receptors. Adapted by permission from Macmillan Publishers Ltd: *Nature*, Brickley et al, 2001.

Are α4/6δ containing GABA$_A$ receptors comparable to the GABA$_C$ receptors in the retina? GABA$_A$ receptors with α6βδ subunits have an EC_{50} values of ~0.5 μM (Saxena & Macdonald, 1996) and slow desensitization constants of ~ 5 seconds (Brown *et al*., 2002). However, these receptors have a shorter burst duration and mean open time than non-δ containing GABA$_A$ receptors (Fisher & Macdonald, 1997), suggesting that they may not mediate more prolonged GABA responses, as GABA$_C$ receptors do. Recombinant and native GABA$_C$ receptors have a similar high affinity to GABA, with an EC_{50} value of ~ 1 μM (Qian & Dowling, 1993; Chang & Weiss, 1999) and show a virtual absence of desensitization during prolonged GABA application. GABA$_C$ receptors also show slow current decay constants,

attributable to very slow unbinding kinetics of the recombinant ρ1 $GABA_C$ receptors when the channel is open (Chang & Weiss, 1999). While the α4/6βδ subtypes of the $GABA_A$ receptor are primarily extrasynaptic and mediate spillover/tonic GABA responses, $GABA_C$ receptors are synaptic (Koulen *et al*., 1998) and mediate slow inhibitory synaptic responses that modulate tonic, graded glutamate release from bipolar cells. Because they have a high affinity for GABA, $GABA_C$ receptors at neighboring synapses may be also be activated by spillover.

Temporally tuning inhibition with distinct GABA receptors

In addition to shaping inhibition by receptor location, GABA receptors with distinct kinetic properties can also temporally tune inhibition. In the retina, the time course of inhibition in different types of bipolar cells is tuned by the relative proportions of $GABA_A$ and $GABA_C$ receptors (Shields *et al*., 2000; Eggers & Lukasiewicz, 2006). In the hippocampus, spontaneous IPSCs in different interneurons have distinct time courses, suggesting that they possess different types of $GABA_A$ receptor subunits (Hajos & Mody, 1997). Additionally, the decay time of GABAerigc IPSCs in many regions of the CNS decreases with development because $GABA_A$ receptor subunits switch from α2 or α5 in early development to α1 containing $GABA_A$ receptors in adults (Brickley *et al*., 1996; Dunning *et al*., 1999; Okada *et al*., 2000, Figure 10). Another example of how different types of receptors temporally tune inhibition comes from the spinal cord and brainstem, where the relative activation of glycine and $GABA_A$ receptors, with distinct kinetics, determines the timecourse of IPSCs (Jonas *et al*., 1998; O'Brien & Berger, 1999). In the retina the kinetics of $GABA_C$ receptor-mediated inhibition are matched to the time course of bipolar cell excitation, as noted above. During development, $GABA_A$ receptor kinetics temporally tune inhibition in a similar way; the timecourse of inhibition decreases in parallel with the decreases in

the time course of excitation that occur during development (Takahashi, 2005).

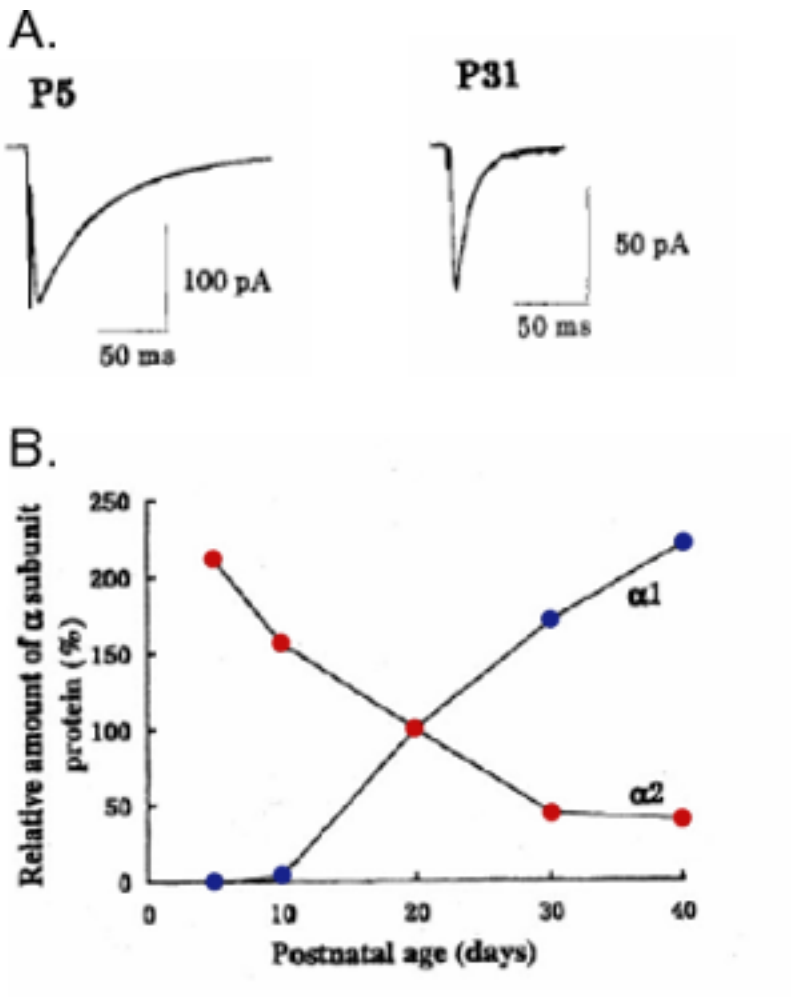

Figure 10. The decay time of GABAergic IPSCs changes over development in the thalamus. A. The decay time constant and rise-time of evoked IPSCs decrease from postnatal day 5 to postnatal day 31. B. Over this same time period, the expression of $GABA_A$ α subunits changes from predominantly α2 to predominantly α1. Reprinted with permission in modified form from Okada et al, 2000, *Journal of Neuroscience*. © 2000 by the Society for Neuroscience.

Modulation of excitatory signaling

Just as $GABA_C$ receptor-mediated currents modulate the temporal and spatial properties of excitatory signaling in the retina, tonic $GABA_A$ receptor-mediated currents (Brickley *et al*., 1996), attributed to

spillover (Hamann *et al*., 2002), decrease the excitability of cerebellar granule cells. This spillover current is significant, mediating the largest amount of inhibitory charge transfer (97%) (Hamann *et al*., 2002). Spillover transmission by distant, extrasynaptic GABA receptors enhances the influence of inhibitory signaling by increasing its spatial extent. This tonic, spillover inhibition reduces spontaneous firing in granule cells by preventing spontaneous excitatory postsynaptic potentials from eliciting action potentials, preserving a high signal-to-noise ratio for the encoding of sensory inputs (Chadderton *et al*., 2004). $GABA_A$ receptors can also play a role in temporal tuning of excitatory responses, similar to the role $GABA_C$ receptors play in the retina, making excitatory responses more transient. In hippocampal pyramidal cells, $GABA_A$ receptor-mediated inhibition decreases the variation in the timing of spiking (Pouille & Scanziani, 2001). This would have the effect, on average, of making signaling from pyramidal cells more transient (Figure 11).

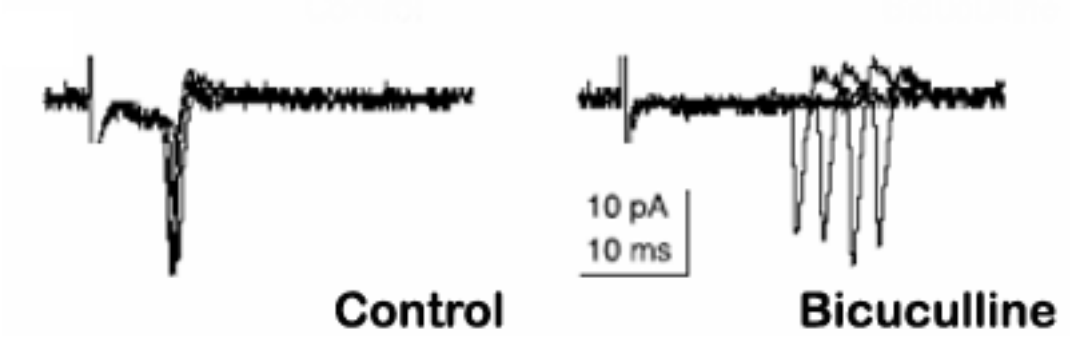

Figure 11. $GABA_A$ receptor-mediated inhibition makes spiking in hippocampal pyramidal cells more transient. Current responses to the stimulation of two separate Shaeffer collaterals recorded from hippocampal pyramidal cells in cell-attached patch mode. In control conditions, a single spike always occurred at the same time over four trials when the 2 Schaeffer collaterals were simultaneously stimulated (left). When inhibition was blocked by the application of bicuculline (right), spiking was no longer synchronized with the stimuli and occurred over a range of times for each of the four stimuli. Reprinted with permission in modified form from Pouille and Scanziani, 2001, *Science*. © 2001, AAAS.

Summary

Ionotropic GABA receptors in the retina and in other parts of the CNS play similar roles. In the retina, slowly responding $GABA_C$ receptors affect the timing and magnitude of transmission from bipolar cells onto ganglion cells, the outputs of the retina. In other parts of the CNS, presynaptic $GABA_A$ receptors modulate release either by autoreceptor-mediated inhibition or by heterosynaptic inhibition. Spillover and tonic inhibition are found in both the retina and other parts of the CNS, but they are mediated by different types of ionotropic GABA receptors, $GABA_C$ receptors in retina and δ and α6/α4 containing $GABA_A$ receptors in the brain The retina is an ideal place to study ionotropic GABAergic inhibition because it can be activated with natural stimuli, the physiological functions of inhibition in sensory processing can be determined, and its inhibitory mechanisms are similar to those found in other parts of the CNS.

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