Nitric Oxide: An Unconventional Messenger in the Nervous System of an Orthopteroid Insect

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Nitric oxide (NO) is a membrane-permeant messenger molecule generated from the amino acid L-arginine. NO can activate soluble guanylyl cyclase leading to the formation of cyclic GMP (cGMP) in target cells. In the nervous system, NO/cGMP signalling is thought to play essential roles in synaptic plasticity during development and also in the mature animal. This paper examines biochemical, cell biological, and physiological investigations of NO/cGMP signalling in the nervous system of the locust, a commonly used neurobiological preparation. Biochemical investigations suggest that an identical enzyme is responsible for both NO synthase (NOS) and NADPH-diaphorase activity after tissue fixation. Immunocytochemical staining of an olfactory center in the locust brain shows that NOS-immunoreactivity colocalizes with NADPH-diaphorase at the cellular level. The cytochemical staining of NO donor and target cells in adult animals suggests functions in olfaction, vision, and sensorimotor integration. During development, NO is implicated in axonal outgrowth and synaptogenesis. The cellular distribution of NO-responsive cells in neural circuits reflects potential functions of NO as a retrograde synaptic messenger, as an intracellular messenger, and as a lateral diffusible messenger independent of conventional synaptic connectivity. Arch. Insect Biochem. Physiol. 48:100–110, 2001. © 2001 Wiley-Liss, Inc.

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INTRODUCTION

Nitric oxide was originally described as the endothelial-derived relaxing factor (EDRF) that accounts for smooth muscle relaxation by vasodilators (Furchgott and Zawadski, 1980). The first demonstration of nitric oxide (NO) as a neuronal messenger came from studies of cerebellar granule cells in which it was shown that activation of N-methyl-D-aspartate (NMDA) receptors by glutamate induced the release of a diffusible messenger with properties indistinguishable from those of EDRF and NO (Garthwaite et al. 1988).

NO is an atypical neurotransmitter since it is not packaged in synaptic vesicles but rather diffuses from its site of production and moves readily through cell membranes. In nerve cells, NO is generated in an activity-dependent process by Ca²⁺/calmodulin-stimulated nitric oxide syn-

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NOS catalyze the production of NO and L-citrulline from L-arginine, O₂, and NADPH-derived electrons. The principal function of NO appears to be as an activator of the heterodimeric heme protein soluble guanylyl cyclase (sGC) (Fig. 1). Binding of nanomolar concentrations of NO to the prosthetic heme group induces sGC to catalyze the formation of cGMP. Despite the fact that NO diffuses in neuropilar compartments the specificity of cellular communication is preserved by the activity-dependent release of the ligand and discrete distribution of the target receptor (Fig. 1). Synthesis of cGMP may directly gate ion channels, stimulate protein kinase G (PKG) and cGMP dependent phosphodiesterases, and regulate additional downstream signal transduction cascades. Since NO is a free radical, cGMP independent signal transduction pathways involving it appear to be also rather common (Stamler et al. 1997).

Compared to the mammalian brain, the simpler nervous systems of insects contain a relatively smaller number of cells, some of which are identifiable individuals. Thus, connections between individual cells can be mapped, an advantageous feature for studying the mechanisms of NO signalling at defined synapses. Neurochemical investigations in fruit flies, locusts, honeybees, and the tobacco hornworm have shown the presence of Ca²⁺/calmodulin-stimulated NOS activity and NO-activated sGC (Elphick et al., 1993, 1995; Müller, 1994; Müller and Bicker, 1994; Qazi and Trimmer, 1999), emphasizing that the cellular mechanisms of NO/cGMP signalling are not peculiar to the mammalian brain but apply to insects as well. In Drosophila and Manduca, the genes encoding a Ca²⁺/calmodulin-dependent NOS and the two subunits of sGC have been cloned (Regulski and Tully, 1995; Liu et al., 1995; Shah and Hyde 1995; Nighorn et al., 1998). Several recent reviews have summarized the functional as-

![Fig. 1. Schematic drawing of transcellular NO/cGMP signal transduction. Neuronal activity in the NO donor cell leads to the influx of Ca²⁺, which stimulates via calmodulin (CaM) the nitric oxide synthase (NOS) enzyme. NOS catalyzes the conversion of arginine into citrulline, which is formed stoichiometrically with NO. This reaction requires nicotinamide adenine dinucleotide phosphate (NADPH) as cofactor. The oxidation of NADPH is visualized in the diaphorase reaction via the reduction of a tetrazolium salt that is precipitated as a blue formazan product. Thus, NOS expressing cells can be identified on tissue sections by NADPHd-histochemistry. In the target cell, NO binds to a heme moiety in soluble guanylyl cyclase (sGC) resulting in the stimulation of the enzyme and consequent elevation of cGMP concentration. cGMP is efficiently down regulated by phosphodiesterases (PDE). sGC expressing target cells can be identified by immunocytochemistry with specific antisera against cGMP. The detection of cGMP-immunoreactivity often, though not always, requires the inhibition of PDE. Since sGC is the most prominent but not the sole target, the described cytochemical method reveals only a subset of neurons that can respond to NO. Drawing adapted from Bicker (1998).]
pects of NO/cGMP signalling in these insect species (Müller, 1997; Bicker, 1998; Enikopolov et al., 1999).

In this paper, I have selected the locust to illuminate some recent work on the neurobiology of NO signalling in insects. The locust is a robust neurophysiological preparation with a nervous system that is built on a clearly segmented plan (reviewed in Burrows, 1996). Lineage studies of identifiable neuronal precursors and nerve cells are available for developmental studies (Goodman and Bate, 1981; Broadus and Doe, 1995). Since adult and larval locust neurons can be readily kept in primary cell culture (Kirchhof and Bicker, 1992), it is also possible to investigate the cellular responses to NO exposure in a controlled environment. Hence, a number of research groups have analyzed the developing and mature nervous system of *Schistocerca gregaria* and *Locusta migratoria*, for aspects of NO signalling during the formation and function of the locust nervous system. With the exception of one embryological study of the neuromuscular system (Ball and Truman, 1998), which reported more cGMP expressing cells in *Schistocerca* than *Locusta*, and hypothesized that this might reflect differing levels of cGMP in the two species, no differences in the anatomical localization of cells involved in NO/cGMP signalling have been reported. In the following text, I will simply refer to the locust.

The formation of NO requires the presence of NADPH as cofactor of the NOS enzyme (Fig. 1). Thus, a simple histochemical method to localize NOS containing cells is to stain fixed nerve tissue for NADPH-diaphorase (NADPHd). As has already been described for mammalian tissue (Matsumoto et al., 1993), the selectivity of this histochemical staining is presumably caused by the resistance of NOS to aldehyde fixation. A basic requirement for identifying NO as a messenger molecule is Ca\(^{2+}\) dependent release during nerve cell depolarization. Using a sensitive photometric assay that measures the binding of NO to the heme group of hemoglobin, it has been demonstrated that dissociated cells obtained from areas of the locust brain enriched in NADPHd positive neurons release NO after stimulation by agents elevating cytoplasmic Ca\(^{2+}\) levels (Müller and Bicker, 1994). Thus, it is likely that NADHd staining reflects NOS expression. Nevertheless, in the absence of biochemical data sound judgment is required to interpret the diaphorase histochemistry. For example, NADPHd staining patterns in wholemounts and on cryosections are dependent on fixation time. This dependence on the fixation protocol may even lead to false-positive results. A comparison of the fixation sensitivity of putatively NOS-related NADPHd in the thoracic ganglia of locusts, crickets, and cockroaches shows that prolonged fixation can induce NADPHd activity in cells that are diaphorase negative under mild fixation regimes (Ott and Burrows, 1999). Using different fixation protocols, the study of Ott and Burrows (1999) has reconciled contradictory findings that neuronal NADPHd in locusts is found exclusively in interneurons (Müller and Bicker, 1994; Ott and Burrows, 1998) whereas in crickets it was also reported in sensory afferents, motoneurons, and efferent dorsal unpaired median neurons (Schümann et al., 1997), concluding that the latter finding does not reflect the situation in the living system, but rather is the result of prolonged fixation.

### NO SIGNALLING IN OLFACTION

To identify NO synthesizing cells in the locust brain, NADPHd-staining was applied on wholemounts and cryosections. The most prominent NADPHd activity in the locust is found in a cluster of 45 to 50 local interneurons of the antennal lobe (Müller and Bicker, 1994; Bicker and Hähnlein, 1995; Elphick et al., 1995), the principal olfactory neuropile of the insect brain. No specific staining was detected in the sensory fibers of the antennal nerve. Analogous to the vertebrate olfactory bulb (Breer and Shepherd, 1993; Shepherd, 1994), the neuropile of the antennal lobe is organized in an array of spherical glomeruli. The strong NADPHd expression in the local interneurons that innervate glomeruli corresponds to the high NOS activity measured in this brain area (Müller and Bicker, 1994; Elphick et al., 1995). In the locust, it has also been possible to localize the NOS enzyme with an antiserum raised to recombinant rat cerebellar NOS showing the same distribution of immunoreactivity in the antennal lobe as that revealed by NADPHd histochemistry (Elphick et al., 1995). In this paper, another
antiserum recognizing a highly conserved sequence of the different mammalian NOS isoforms was used. Again, this antiserum labels the somata and glomerular arborizations of the local interneurons. As shown in Figure 2, there is a clear co-localization of NOS-immunoreactivity with NADPHd activity on double-stained cryosections, supporting the molecular identity of diaphorase and NOS enzymes in the antennal lobe.

Cellular targets can be identified by the capacity of NO to stimulate cGMP synthesis (Fig. 1). After exposure of the nervous tissue to chemicals releasing NO, the accumulation of cGMP can be visualized with specific antisera to cGMP (De

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**Fig. 2.** Locust antennal lobe in a frontal view. Nervous tissue was fixed for 1.5 h in 4% formaldehyde in phosphate-buffered saline (PBS, pH 7.4). The cryosection of the antennal lobe was double-labelled for NADPH-diaphorase (NADPHd) according to Seidel and Bicker (1997) and for universal NOS-immunoreactivity (uNOS-IR). The rabbit polyclonal anti-universal NOS antiserum was used according to the instructions of the manufacturer (Affinity Bioreagents, Inc., Golden, CO) and detected using immunofluorescence. NADPHd staining and immunofluorescence are co-localized in the cell body cluster of the local interneurons at the lower left border and in the glomerular neuropile of the antennal lobe. The micrographs, courtesy of Claudia Seidel, have not been published previously. Scale bar = 100 μm.
However, it should be emphasized that even though stimulation of sGC is a major transduction pathway of the NO signalling cascade, other transduction pathways that signal through redox events are possible (Stamler et al., 1997). Thus, exogenous stimulation of sGC with NO can only reveal a subset of neurons that in vivo are responsive to NO.

In the locust antennal lobe, the majority of NADPHd positive local interneurons express NO-induced cGMP immunoreactivity, suggesting that NO may not only act as a transcellular but also as an intracellular messenger in insect olfactory circuits (Bicker et al., 1996, 1997) or that all of the cGMP expressing neurons are connected in an interacting network, as discussed below. All of the NO-releasing local interneurons in the antennal lobe of the locust appear to use GABA as a conventional transmitter (Seidel and Bicker, 1997).

Electrophysiological studies have detected odor-evoked synchronization of neural activity in olfactory pathways, which can be blocked by interfering with GABAergic neurotransmission (Laurent, 1996; MacLeod and Laurent, 1996). Since the GABAergic olfactory interneurons are sources and targets of NO, it remains a distinct possibility that NO mediated signalling may operate in parallel to the conventional synaptic transmission to synchronize neural activity. Such a coordination of field potential oscillations has been demonstrated by pharmacological manipulations of NO levels in the olfactory system of a mollusc (Gelperin, 1994). NO signalling and synchronized neural activity appear to be a rather common feature of olfactory information processing in insects, molluscs, and vertebrates (Breer and Shepherd, 1993; Gelperin, 1999).

The second major relay station of the olfactory information processing pathways in insects is the mushroom body, which receives sensory input from the antennal lobe via the projection neurons. Experimental evidence largely supports a complex role of mushroom bodies in certain forms of olfactory conditioning, even though the detailed synaptic mechanisms remain unknown (Heisenberg, 1998). Fibers of the mushroom body intrinsic Kenyon cells project from their calycal input area in a parallel arrangement through the pedunculus and finally branch into a reascending a-lobe and the medial b-lobe. The pattern of NADPHd-expression in the mushroom bodies is strictly compartmentalized. Whereas the predominant output regions of the lobes and pedunculus are densely invaded by fine granular staining, the input regions of the calyx are not stained (Bicker and Hähnlein, 1995). As has been reported for Drosophila and Apis (Müller, 1994), the Kenyon cells of the locust do not stain for NADPHd. The pedunculus contains remarkably organized fine granular staining that is thought to be caused by cellular processes originating extrinsic to the mushroom body because the somata of the Kenyon cells and their dendritic arborizations in the calyx do not express NADPHd activity (Müller and Bicker, 1994; Bicker and Hähnlein, 1995). In the a-lobe, O’Shea et al., (1998) have identified six tubular structures of NADPHd stained material that enclose unstained bundles of Kenyon cells. A model calculation of the temporo-spatial diffusion of NO generated by synthesis from the wall illustrated that after an initial period when the NO concentration peaks within the tube wall, a far greater concentration is to be found within the center of the structure than at a similar distance outside the wall of one of those tubes (O’Shea et al., 1998). This would permit lateral interactions throughout the diffusion-defined tubular domains in the mushroom body. Intriguingly, the concentration of NO in the center of such a “gas pipeline” represents a trace of past activity in the tube walls that may influence in a time-delayed process the neural activity of Kenyon cell bundles in separate compartments of the mushroom body. This feature fits well in a functional role of the mushroom body in associative learning mechanisms that have to be critically sensitive to the temporal ordering of synaptic activity. Diffuse neuromodulatory signalling systems have been implicated in predictive learning rules (Montague and Sejnowski, 1994). The neural architecture of the NO releasing tubular domains may thus provide an anatomical substrate for “volume learning mechanisms” that have been postulated on theoretical grounds. It is indeed conceivable that in vivo NO may be released onto Kenyon cells from neurons extrinsic to the mushroom body, since NO-induced cGMP-IR has been found in bundled subsets of Kenyon cells (Bicker et al., 1996).
NO SIGNALLING IN INSECT GLIAL CELLS

When exposed to bacterial lipopolysaccharides or cytokines, mammalian astrocytes display both constitutive and/or inducible NOS activity (Murphy et al., 1993). Using NADPHd-histochemistry as a marker for NOS, staining has also been detected in glial cells of the locust brain (Bicker and Hähnlein, 1995). In the mushroom bodies, various subgroups of glial cells can be identified on the basis of their size, shape, and location. A layer of glial cells separates the calycal neuropile from the surrounding protocerebral neuropile (Hähnlein et al., 1996). The cell bodies of NADPHd positive glial cells either line the neuropile or are interspersed among the somata of the mushroom body intrinsic Kenyon cells. Sections cut through the pedunculus show large NADPHd-positive glial cells enclosing the neuropile, which are, however, not as intensely stained as the glial layer around the calyx. Since NO is a membrane permeable messenger, glial-derived NO should be capable of influencing neighbouring neuronal processes in the mushroom body neuropile. Moreover, the co-expression of cGMP-IR (Bicker et al., 1996) and NADPHd staining (Bicker and Hähnlein, 1995) in glial cells lining the mushroom bodies suggest the NO/cGMP signalling system as a component of glial communication in an insect brain.

NO SIGNALLING IN VISION

Since Ramón y Cajal formulated the principle of dynamic polarization of the neuron at the turn of the century, every chemical synapse investigated has proven unidirectional. NO has changed our view of unidirectional information flow in the nervous system. A remarkable feature of retrograde NO signalling is that the postsynaptic Ca\textsuperscript{2+} influx during conventional synaptic transmission can cause the generation of a NO message that spreads to presynaptic cells. In this mode of bidirectional transmission, a NO-responsive presynaptic neuron is informed about the ongoing neuronal activity in its postsynaptic partner leading to changes in the presynaptic transmitter release. For example, the genetic knockout of NOS isozymes, membrane targeting of a specific NOS isoform, and the experimental manipulation of NO signalling at isolated synapses in primary culture, support the idea that NO serves as a retrograde messenger during long-term potentiation in the mammalian hippocampus (Arancio et al., 1996; Kantor et al., 1996; Son et al., 1996).

Cytochemical investigations in the optic lobe of locusts indicate that such a retrograde signalling pathway may also exist between the photoreceptor cells of the compound eye and their postsynaptic first order interneurons, the monopolar cells of the lamina. Since 40% of the monopolar cells express strong NADPHd staining (Elphick et al., 1996; Bicker and Schmachtenberg, 1997) they represent a likely source of NO. When tissue preparations of the optic lobes are exposed to NO, the accumulation of cGMP can be demonstrated in the presynaptic photoreceptor cells but not in other postsynaptic cellular targets in the vicinity of the monopolar cells (Bicker and Schmachtenberg, 1997). Using affinity-purified antibodies to an evolutionarily conserved sequence of the Drosophila α-subunit of sGC, Elphick and Jones (1998) have also localized immunoreactivity to the locust photoreceptor cells. The antibody has revealed particularly striking immunoreactivity in the rhabdomere, where the phototransduction process occurs, whereas the photoreceptor axons entering the lamina are rather weakly stained (Jones and Elphick, 1999). In fly photoreceptors, cGMP is one of the activators of pigment granule migration, a cellular process that is triggered separately from phototransduction (Hanyu and Franceschini, 1993). Cyclic-GMP mediated pigment granule migration may, thus, contribute to the regulation of light flux in rhabdomeric photoreceptors.

To demonstrate that locust photoreceptor neurons are potential targets of an endogenous NO release system, electrophysiological recording has been used to monitor the effects of drugs affecting NO/cGMP signalling. Application of drugs raising NO/cGMP levels in the optic lobe increases photoreceptor sensitivity, whereas the experimental reduction of NO levels caused a decrease in the light response (Schmachtenberg and Bicker, 1999). In conclusion, both the cytochemical and electrophysiological data are consistent with the hypothesis that NO synthesized in monopolar cells is a retrograde messenger to the presynaptic photoreceptor neurons. Such retrograde synaptic information transfer may be used during
dark adaptation processes. Recent biochemical measurements have indeed shown that NO stimulates the production of cGMP in dark but not in light adapted eyes of the locust (Jones and Elphick, 1999). The inhibitory effect of light and increased Ca$^{2+}$ levels on cGMP synthesis suggests that light-induced Ca$^{2+}$ fluxes may regulate sGC activity in locust photoreceptors.

In the depolarizing insect photoreceptors, cGMP is generally not considered an integral part of the phototransduction process. Rather, there is increasing evidence that the opening of light-sensitive channels in the plasma membrane of Drosophila photoreceptor cells involves an activation of the phosphoinositide cascade and the formation of polyunsaturated fatty acids (Ranganathan et al., 1995, Zuker, 1996; Chyb et al., 1999). However, the presence of a retrogradely acting NO/cGMP system might explain the enigma of why in rhabdomeric photoreceptors of insects, homologues of the vertebrate cGMP-gated ion channel (Baumann et al., 1994, Bacigalupo et al., 1995) and sGC (Shah and Hyde, 1995) have been found. In addition, the distinct cellular distribution of NADPHd expressing neurons in the other ganglia of the locust optic lobe (Elphick et al., 1996; Seidel and Bicker, 1997) suggests many other important roles of NO at several stages of insect visual information processing.

NO SIGNALLING IN SENSORIMOTOR CIRCUITS

The presence of an NADPHd-stained projection neuropile of the thoracic mechanosensitive afferents suggests a role for NO in the processing of mechanosensory information in locusts, crickets, and cockroaches (Ott and Burrows, 1998, 1999). This staining could be attributed to intersegmental interneurons that may release NO onto the afferents of sensorimotor circuits. Thus, retrograde NO/cGMP signalling is also implicated in mechanosensory information processing. Moreover, immunocytochemical studies of the brain have localized the $\alpha$ subunit of sGC in mechanosensory afferents of the antenna (Elphick and Jones, 1998). Using two complementary approaches, Ott et al. (2000) compared immunostaining for the $\alpha$ subunit of sGC with NO-induced c-GMP immunoreactivity, showing that both sensory afferents and motoneurons of the thoracic ganglia contain functional sGC. Physiological investigations of the larval neuromuscular system in Drosophila (Wildemann and Bicker, 1999b) and the crayfish (Aonuma et al., 2000) have uncovered modulatory effects of nitric oxide on synaptic transmission in the peripheral nervous system. Based on the finding that visual, chemosensory, and mechanosensory modalities are targets for NO, Ott et al. (2000) suggested a general role for NO/cGMP signalling in dynamic cross-adaptation or cross-sensitization processes among sensory channels with adjacent projections.

NO SIGNALLING DURING DEVELOPMENT

Experimental manipulations of NO signal transduction and the dynamic regulation of NOS during the formation of the nervous system implicate NO signalling in developmental mechanisms of the vertebrate nervous system (Wu et al., 1994; Cramer et al., 1996; Wang et al., 1995). There is also accumulating evidence that NO/cGMP signalling participates in developmental processes of the locust. In embryonic grasshoppers, synaptogenesis correlates with a phase when many identifiable nerve cell types respond to nitric oxide by producing cGMP (Truman et al., 1996; Ball and Truman, 1998). Some of these are identified motoneurons, the axonal growth cones of which can be stained for cGMP-IR. The sensitivity to NO appears after the growth cone has arrived at its target but before branches have started to explore the muscle, reflecting the transition from longitudinal elongation to the formation of lateral branch growth. Thus, Ball and Truman (1998) suggested that cGMP plays a role in the early stages of communication between a postsynaptic target and specific innervating neurons. With the exception of the slow extensor tibiae motoneuron, the first motoneuron to reach any muscle is, however, not NO responsive. In Ball and Truman’s (1998) detailed study, they observed a slight species specific difference in cGMP response from the slow and fast extensor motoneurons in Locusta and Schistocerca.

NO-induced cGMP-IR is by no means restricted to motoneurons. For example, certain sensory and interneurons also become NO receptive as they change from axonal outgrowth to synap-
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During synaptogenesis and synaptic maturation. Other examples of the dynamic regulation of NO-induced cGMP formation during synaptic maturation have been described at the larval neuromuscular junction of Drosophila (Wildemann and Bicker, 1999a,b).

Since adult motoneurons do also express NO sensitive sGC (Ott et al., 2000), it might be rewarding to explore the functional relationship of NO signal transduction during synaptogenesis to its role in the mature neurotransmission. Does, for example, NO/cGMP signal transduction controlling synaptic efficacy during neurotransmission recapitulate ontogenetic programs during synapse formation and maturation? The developing photoreceptors of the embryonic compound eye express NO-induced cGMP-IR (Truman et al., 1996). Thus, the photoreceptor neurons can serve as a second example for the provocative hypothesis that NO is a molecular mediator of neuroplasticity in the same cell populations of the developing (Truman et al., 1996) and mature nervous system (Bicker and Schmachtenberg, 1997).

Intriguingly, experimental manipulations of NO/cGMP signal transduction during the period of NO sensitivity in Drosophila disrupted the establishment of proper retinal connections in the optic lobe (Gibbs and Truman, 1998). In essence, the NO sensitive insect photoreceptors appear to employ the cellular machinery of a retrograde NO/cGMP signalling system in two different functional contexts: for transcellular signalling during synaptogenesis in the embryo and to adjust the light sensitivity in visual information processing of adult stages.

The body appendages of grasshopper embryos have provided a useful model system for the study of pathfinding mechanisms during growth cone navigation of identified pioneer neurons (Bentley and O’Connor, 1992). Pathfinding seems to involve both selective adhesion of the growth cones to substrate bound guidance cues provided by the epithelial cells and recognition of guide post cells. A recent investigation has identified a novel member of the semaphorin family, which is expressed in a gradient in the developing limb bud epithelium and acts as a chemorepulsive guidance molecule (Ishibister et al., 1999). Similar to the appendages of the thoracic segments, the first neural pathways in the antenna of the grasshopper are established by identified pairs of pioneer neurons (Bate 1976; Ho and Goodman, 1982). These pioneer neurons synthesize cGMP in response to exogenous NO treatment (Seidel and Bicker, 2000). Pharmacological inhibition of endogenous guanylyl cyclase and of NO synthase activity in embryo culture results in an abnormal pattern of pathway formation in the antenna. The pharmacological disruption of pioneering pathways can be rescued by supplementing with membrane permeant cGMP, suggesting that the growth cone may receive a NO signal from surrounding tissue and that the elevated cGMP levels are critical for axonal growth toward the CNS (Seidel and Bicker, 2000).

Cell culture experiments with dissociated Xenopus spinal neurons have shown that elevated levels of cGMP can convert the response of growth cones to a semaphorin from repulsion to attraction (Song et al., 1998). Remarkably, an asymmetric cellular localization of sGC to the dendrite of pyramidal cells is thought to confer the opposite directional outgrowth to dendrites and axons in a semaphorin gradient of the cerebral cortex (Polleux et al., 2000). Thus, intracellular cyclic nucleotide levels may serve the purpose of modulating the directional behavior of growth cones in response to other chemotropic guidance cues.

In this paper, I have focussed on NO as a mediator of neural processes in a rather simple hemimetabolous insect. These neurobiological studies have been aided by several decades of accumulating knowledge about identified neurons in the developing and mature locust nervous system (e.g., Bate, 1976, Goodman and Bate, 1981; Bentley and O’Connor, 1992; Burrows, 1996). It is also clear, however, that the freely diffusible gas NO is involved in a scope of physiological processes touching on the functions of almost any organ in the animal body.

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LITERATURE CITED


