A review of the actions of Nitric Oxide in development and neuronal function in major invertebrate model systems

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Abstract: Ever since the late-eighties when endothelium-derived relaxing factor was found to be the gas nitric oxide, endogenous nitric oxide production has been observed in virtually all animal groups tested and additionally in plants, diatoms, slime molds and bacteria. The fact that this new messenger was actually a gas and therefore didn’t obey the established rules of neurotransmission made it even more intriguing. In just 30 years there is now too much information for useful comprehensive reviews even if limited to animals alone. Therefore this review attempts to survey the actions of nitric oxide on development and neuronal function in selected major invertebrate models only so allowing some detailed discussion but still covering most of the primary references. Invertebrate model systems have some very useful advantages over more expensive and demanding animal models such as large, easily identifiable neurons and simple circuits in tissues that are typically far easier to keep viable. A table summarizing this information along with the major relevant references has been included for convenience.

Keywords: nitric oxide; neuronal development; neuronal function; insect; mollusc; crustacean

1. Introduction

Ever since the late-eighties when endothelium-derived relaxing factor (EDRF) was found to be the gas nitric oxide (NO) [1–3] endogenous NO production has been observed in virtually all animal groups tested and additionally in plants, diatoms, slime molds and bacteria [4–8]. The fact that this new messenger was actually a gas and therefore didn’t obey the established rules of neurotransmission made it even more intriguing. Research into this novel new player has expanded rapidly especially in the field of neuroscience with NO being implicated in such significant and
wide-ranging processes as olfaction, learning and memory and dementia. In neuroscience invertebrate models have always been held in high regard because the nervous systems are simpler and typically composed of large peripherally-arranged cell bodies that can often be identified from preparation to preparation so ensuring the utilization of the same neuron in each experiment. This review is focused on the direct effects of NO on invertebrate neurons and nervous systems and additionally neuronal developmental in which NO has been implicated. A review of all the invertebrate organisms utilized for NO research, let alone all animals, would probably be overwhelming so for this review the groups covered will be limited to the major model organisms from the molluscs, insects and their watery cousins the crustaceans. This still leaves a significant number of organisms to cover especially as, for example, there are several different species of land snail utilized by researchers around the world. The author himself used *Helix aspersa* because they were easy to collect locally (and free!) in and around the University of Southampton in England where he performed his PhD. under the direction of Dr. R.J. Walker. Where possible the individual species are discussed but if too numerous they are grouped appropriately. Hopefully the majority of research utilizing these animals has been included and additionally compiled into a comprehensive table for easy reference (Table 1). It is hoped that this review can help guide the reader to the primary literature on the appropriate model system for a detailed description which would be beyond the scope of this review.

2. **Nitric oxide**

Before discussing the possible effects of NO on these selected invertebrates' neurons and nervous systems, it might prove useful to briefly discuss the origins and chemistry of NO; for a far more comprehensive overview the reader is recommended to access Moroz and Kohn’s excellent 2011 review [9]. That review suggests NO involvement in signaling is traceable back to the origins of life. Nitric oxide is in fact part of the nitrogen cycle and a vital intermediate which is far more reactive than nitrogen itself which has to be “fixed” before most organisms can utilize it [10–15]. It should be noted that “nitric oxide” actually includes the nitrosyl radical itself plus the nitroxy1 and nitronium ions [16–19]. Nitric oxide is quite reactive and can form covalent bonds with many biological molecules including its primary target guanylate cyclase; this is significant in itself as most signal transduction interactions do not involve formal covalent bond formation. As a hydrophobic gas NO can cross biological membranes easily and because of this it is considered to act as a “3-D” volume messenger unlike conventional transmitters that are typically limited to synaptic locations for transmission [20–24]. Additionally it can be appreciated that NO levels are affected by the redox status of a cell and there appears to be a complex relationship with oxygen gradients and so-called “metabolic budgets” [25,26]; this may have been an early function of NO in biological systems. There is data linking NO to mitochondrial function [27–36] and its half-life can be quite variable ranging from a few milliseconds to days depending on the chemical environment [9]. Despite this NO is considered a relatively short-range messenger acting in an autocrine and/or paracrine manner. These factors help explain why direct measurement of NO in living tissues is difficult. This has resulted in the development of a plethora of methods for NO detection and quantification. Although not the primary focus of this review it is probably useful to mention and provide references here to the main techniques for NO detection in living tissues. One of the first methods available to invertebrate neurobiologists utilized NO-sensitive electrodes and was rapidly
followed by fluorometric detection, spin-trapping and even capillary electrophoresis at the single cell level [37–55]. Probably in all invertebrate species examined the first task was not the detection of endogenous NO production but the far easier demonstration of the presumed primary source of NO in biological systems, namely the enzyme nitric oxide synthase (NOS). Initially this was demonstrated by NADPH-diaphorase histochemistry and is invariably cited in virtually all of the physiological function papers tabulated here (Table 1), many of which demonstrated NOS expression almost as a prerequisite to observing any effects NO might have. Again, the reader is referred to other sources for a proper discussion of this technique [56–59]. In 1990 Snyder’s research group isolated and purified so-called neuronal NOS (nNOS) from rat cerebella and used this to develop antibodies for immunohistochemical localization [60,61]. Finally it should be noted that there are in fact at least 7 potential enzymatic sources of NO production in living organisms. These include the so-called “classic” multi-domain NOS’s found in animals and slime molds [62,63], a prokaryotic “truncated” NOS found in many bacteria [7,64] and various nitrite reduction systems [7,28,65–73].

3. Nitric oxide synthase

Despite multiple potential sources, the principal source producing NO in animals, including the subjects of this review, is the family of “classic” multi-domain NOS’s. As mentioned, the first constitutive NOS isoform was cloned from rat brain (nNOS) 4 years after the discovery that EDRF was NO in 1991 [74]. One year later 2 other isoforms were cloned; an inducible type (iNOS) from macrophages [75–77] and a second constitutive type (eNOS) from endothelium [78–82]. All 3 NOS’s were similar to cytochrome P450 with reductase and oxygenase domains. It is thought parallel evolution occurred from a single truncated NOS a billion years ago and while iNOS is calcium independent, nNOS and eNOS are calcium-calmodulin dependent [83,84]. In all animal tissues NOS catalyzes NO production from a reaction between L-arginine and molecular oxygen with the release of L-citrulline [62,63]. In 1991 the first evidence for the function of NO in invertebrates (Limulus; the horseshoe crab) was published [85] quickly followed the next year by NOS histochemistry revealing widespread expression in several major invertebrate phyla including molluscs and arthropods. Currently it is thought that insects have one NOS gene while molluscs have two [56]. The two calcium-calmodulin dependent NOS’s (nNOS and eNOS) are activated by elevated intracellular calcium typically either from ligand- or voltage-gated calcium channels or internal stores. Inducible NOS is expressed and activated in the presence of bacterial lipopolysaccharides or damaging stimuli [9].
Table 1. This table attempts to summarize the material discussed in this review including the animals comprising each of the groups, the main research topics studied and the principal references.

| Number | Group | Source Refs | Subjects Covered |
|--------|-------|-------------|------------------|
| **INSECT DEVELOPMENT** | | | |
| Locusta migratoria, Schistocerca gregaria (locust) | 11 | GP1 100–110 | Embryonic development, neuronal migration, growth cone function and synaptogenesis. |
| Drosophila melanogaster (fruit fly) | 14 | GP2 111–124 | Adult development, visual system development, growth cone/filopodial function and tracheal development/response to hypoxia. |
| Manduca sexta (moth) | 8 | GP3 125–132 | Development at all stages, sensory system development (olfactory and visual), neuronal migration, differentiation and arborization. |
| Gryllus bimaculatus | 1 | GP4 133 | NO involved in environmentally-induced neurogenesis in the mushroom bodies. |
| **INSECT NITRIC OXIDE** | | | |
| Apis mellifera (honeybee) | 5 | GP5 134–139 | Established learning and memory system/proboscis extension for sucrose reward, NO involved at several levels of olfaction (Mushroom bodies and Antennal lobes). |
| Locusta migratoria & gregaria (locust) | 16 | GP6 140–155 | NO affects several sensory modalities and motor pattern responses, heart regulation; neuropil architecture suits 3-D "volume transmitter" (= gas). |
| Manduca sexta, Bombyx mori (moth) | 9 | GP7 156–164 | NO involved in odor perception/short-term memory formation (enhance inward currents), variations with circadian rhythm, interactions with nicotinic receptors. |
| Drosophila melanogaster (fruit fly) | 4 | GP8 165–168 | Retrograde transmitter at larval neuromuscular junction/vesicle release, NO-cGMP implicated in Antennal lobe function/projection neurons. |
| Lampyridae (firefly), Neobellieria bullata (fleshfly), Phormia regina (blowfly), Chorthippus biguttulus (grasshopper) | 4 | GP9 169–172 | NO in fireflies controls flashing, cGMP in taste in blowflies and NO in olfaction in fleshflies. |
| Gryllus bimaculatus (cricket) | 6 | GP10 173–176 | No and cGMP involvement in central complex sound production and in juvenile hormone release (reproductive function). |
| Periplaneta Americana, Blaberus craniifer (cockroach) | 6 | GP12 148,184–188 | Allosteryism of sGC, estradiol affects NO production, NO affects nicotinic currents and long-term memory. |
| **MOLLUSC DEVELOPMENT** | | | |
| Lymnaea stagnalis (pond snail) | 3 | GP13 189–191 | NO involved in embryonic development, neurite growth and synaptic re-modelling after injury, NO implicated in locomotion, heartbeat and feeding. |
| Helisoma trivolvis (pond snail) | 11 | GP14 122,192–201 | NO affects growth cone function via sGC, cGMP, Ca²⁺ (internal source) and PKG; NO chemotactic for pathfinding, affects K⁺ currents and ciliary function plus causes ADP-ribosylation. |
| Ilyanassa obsoleta (sea snail) | 2 | GP15 202–203 | |
| MOLLUSC NITRIC OXIDE                                                                 | Number | Group | Source Refs | Subjects Covered                                                                                                                                 |
|-------------------------------------------------------------------------------------|--------|-------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Land snails                                                                         | 22     | GP16  | 204–227     | Peptides, membrane currents, analgesia, hypoxia, cold, nociception, synaptic and retrograde transmission, olfaction, activity vs rest and memory.       |
| Limax Maximus, Limax Valentinus, Limax Marginatus (land slug)                       | 8      | GP17  | 228–235     | NO-cGMP affects olfaction, discrimination and learning and memory in the oscillating procerebrum of this established odor processing model.          |
| Lymnaea stagnalis, Helisoma trivolvus, Planorbarius corneus (pond snails)           | 25     | GP18  | 215,226,236–258 | Feeding behavior and rhythmic activity in buccal ganglion, internal Ca^{2+} release, synaptic transmission, long-term memory and conditioning, response to glutamate and iNOS expression. |
| Stramonita haemastoma (sea snail)                                                   | 2      | GP19  | 259 & 260   | NO associated with sensory afferents and response to environmental stress.                                                                   |
| Crenomytilus grayanus, Mytilus edulis, Pecten irradians (bivalve molluscs)           | 6      | GP20  | 261–266     | Transcutaneous electrical nerve stimulation (TENS) system model for pain, neuroprotective mechanisms for temperature, hypoxia and pollution, NO involved in ciliary activity regulation. |
| Aplysia (and other sea slugs)                                                       | 24     | GP21  | 267–289     | Feeding/swallowing, NO affects buccal ganglion, modulates/affects dopamine, acetylcholine, glutamate, histamine and Met-encephalin-induced membrane currents plus directly depolarizes and neuropathic pain model. |
| Crustacean Development                                                               | 2      | GP22  | 290 & 291   | NO in development and injury of olfactory system, Stomatogastric ganglion responsiveness, possible involvement in transcription.                    |
| Crustacean Nitric Oxide                                                              | 4      | GP23  | 292–295     | NO and neuropeptides in heart control.                                                                                                         |
| various Crabs                                                                       | 6      | GP24  | 296–301     | Pigment in the retina, nociceptive stimuli processing and somatogastric ganglion activity.                                              |
| Pacifastacus leniusculus (crayfish)                                                 | 12     | GP25  | 302–313     | Glial cell apoptosis (Photodynamic therapy), sensory processing and plasticity and retrograde synaptic transmission at the neuromuscular junction. |
| Calanus finmarchicus (zooplankton)                                                 | 1      | GP26  | 314         | N/A                                                                                                                                            |

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4. Nitric oxide effectors

As mentioned earlier, the primary mechanism of action of NO is thought to be via the activation of soluble guanylate cyclase (sGC) which produces the secondary messenger cyclic guanosine monophosphate (cGMP) [86]. The term soluble is probably not ideal as at least one isoform of GC is thought to actually bind to PDZ domains of synaptic scaffolding proteins so is not “free” in the cytoplasm as the name implies [87]. Guanylate cyclase is a dimeric enzyme with 2 subunits and an NO-binding heme group [88]. The covalent binding of NO to sGC causes the production of cGMP from GTP [89]. Cyclic GMP can then activate several major types of effectors including cGMP-dependent protein kinases (PKGs), cGMP-gated ion channels and various phosphodiesterases which also degrade cGMP back to GMP; the reader is referred to the review by Francis et al. for an in-depth discussion of this topic [90]. Additionally NO can covalently react with redox-sensitive cysteine residues in many proteins causing S-nitrosylation which can cause, for example, changes in enzyme activity, protein-protein binding, membrane targeting, transport systems and protein folding and stability. Currently around 3000 different affected proteins have been identified [91–99].

5. Actions of nitric oxide on invertebrate model systems

The remainder of this review will attempt to summarize the actions of NO on selected invertebrate model systems, specifically molluscs, insects and their watery cousins the crustaceans. Additionally the table (Table 1) will present much of this data in a more accessible form complete with selected references. Each “family” (molluscs vs. insects vs. crustaceans) is divided into developmental or direct effects of NO on neurons and nervous systems and then further divided into groups (together with their selected references; see Table 1) of either individual species or closely related species depending on the amount of research performed utilizing that species; there are 26 groups in total.

6. Insect development (Groups 1–4)

Group 1 involves developmental research utilizing locusts and the effects of NO (Locusta migratoria and Schistocerca gregaria). In the embryonic locust the NO-cGMP system is permissive for neuronal development and migration (antagonized by carbon monoxide); research using the enteric nervous system has produced videos of actual neuronal migration. It is implicated in the development of the central complex which is thought to be involved in spatial orientation/awareness. Nitric oxide also affects axon growth and regeneration in locusts including growth cone function, synaptogenesis and neuronal maturation [100–110].

Group 2 includes development observed in Drosophila melanogaster (fruit fly). The NO-cGMP system is essential for proper development, specifically affecting neuronal proliferation, remodelling, specificity and differentiation. Nitric oxide-cGMP is strongly implicated in the development of the visual system including effects on growth cone filopodia and may act as a retrograde transmitter at neuromuscular junctions (NMJ’s) and in eye development. The NO-cGMP-PKG system is used by fruit flies in response to hypoxia [111–124]. Group 3 concerns the moth Manduca sexta. The NO-sGC-cGMP system is implicated in all stages of development from embryo
to larva to pupal/adult. Nitric oxide is thought also to be involved in neuronal migration, differentiation and arborization. In particular NO appears necessary for the development of various sensory systems including the visual system and the antennal lobes (AL’s)/olfactory system. Nitric oxide also stimulated motorneurons and was involved in the development and migration of the peripheral nerve plexus which gives rise to neurons in the ventral nerve cord in the larval stage. It is worth noting that Gibson et al. reported disruption of AL development after blocking NO-mediated ADP-ribosylation [125–132]. Group 4 used the cricket Gryllus bimaculatus as a model system. It may have been more appropriate to place this in group 1 with its larger relatives but Cayre et al. nicely demonstrate that endogenous NO has a key role in environmentally-induced neurogenesis of the mushroom bodies (MB’s), structures thought to be involved in associative learning in insects [133].

7. Insect physiology (Groups 5–12)

The next 8 groups (5–12) summarize the direct effects of NO on neurons and nervous systems of insects. Group 5 involves research on Apis mellifera (the honey bee). The honey bee is an established associative learning and habituation model system, typically monitoring proboscis extension to a sucrose reward. This response may actually involve activation of PKA as opposed to PKG by the NO-cGMP system. In the AL’s NO manipulation can affect odor discrimination. Mushroom body neurons in vitro show increases in intracellular calcium with nitric oxide confirming NO’s significance throughout this insect’s olfactory system. Nitric oxide also appears crucial for the conversion of short into long term memory [134–139]. Group 6 summarizes direct effects of NO on neurons and nervous systems of locusts (Locusta migratoria and Schistocerca gregaria). Here NO has been implicated in several important functions such as affecting motor patterns for feeding and egg laying and regulating the heart. Nitric oxide appears to be involved in several sensory modalities including taste, olfaction and vision; NO is implicated in significant sensory and motor function in the locust. Apparently the chemosensory response to NaCl is regulated by NO as is the response of leg hairs to mechanical stimulation. The response to salt is thought to be cGMP-independent and research involving the cockroach and locust has suggested allostetism occurring in the response of sGC to NO. Interestingly, NO has been shown to affect spreading depression in the locust metathoracic ganglion via the cGMP-PKG system; if activated, spreading depression is increased. Of particular significance is the research that suggests NO’s ability to act as a 3-D “volume transmitter,” due to it being a gas, suits the physical arrangement of ganglia neuropil in the locust [140–155]. Group 7 utilizes moths to study the effects of NO (2 species here; Manduca sexta and Bombyx mori). This group focuses on olfaction primarily and increases in NO with odor stimulation can be observed in the AL’s projection neurons in an apparently sGC-independent manner (an NO-insensitive sGC has been isolated and may be necessary for a response to hypoxia. Using the established larval wall NMJ preparation, NO has been implicated as a
retrograde transmitter capable of increasing cGMP levels in pre-synaptic terminals and enhancing vesicle release in a calcium-independent manner. Nitric oxide is again implicated in AL projection neuron function with increasing NO levels decreasing cholinergic spontaneous excitatory postsynaptic potentials [165–168]. The next group (9) contains some rarer but novel fly models (Photinus and Photuris fireflies, the blowfly Phormia regina and the fleshfly Neobellieria bullata). Nitric oxide appears to mediate neuronal control of flashing in fireflies while in blowflies taste receptors may use cGMP for signal transduction. The fleshfly also probably uses NO in olfaction [169–172]. Group 10 looks at NO in Chorthippus biguttulus (grasshopper); I have separated locusts, grasshoppers and crickets for the sake of this review. This model was used extensively by the Heinrich group to look at central complex function specifically with respect to producing the appropriate sound production for reproduction. Disruption of the NO-cGMP system affects this function; if the environment is unsuitable for reproduction, elevated NO raises the behavioral threshold for sound production. The endocrine gland the corpora allata releases juvenile hormone also necessary for reproduction; NO and cGMP may be involved with NO possibly acting as a retrograde transmitter [173–176]. Group 11 looks at NO in the cricket Gryllus bimaculatus. It was found that long term memory formation may be due to PKA being activated by cGMP via adenylyl cyclase and cyclic adenosine monophosphate unlike the situation observed in the honeybee [139,177]. Mushroom body neurogenesis appears affected by NO which also increases the probability of calcium channel opening in the principal MB neurons the Kenyon cells; the mechanism here may involve PKG. Apparently submissive behavior in the cricket may involve NO [178–183]. The cockroach was utilized by researchers in group 12 (Periplaneta Americana) and Ott et al. demonstrate that in both the cockroach and locust sGC activity can be increased via an allosteric, NO-independent mechanism as observed in mammals. An estradiol found in many animals can apparently modify NO production in the giant cockroach (Blaberus craniifer). Nitric oxide-cGMP-PKG can affect nicotinic currents in these animals and NO is implicated in MB function yet again. In fact disruption of NO production appears to impair long term but not short term memory. The modulatory Dorsal Unpaired Median cells (DUM) display increased calcium entry with increasing cGMP levels [148,184–188].

8. Molluscan development (Groups 13–15)

Group 13 used Lymnaea stagnalis (pond snail) to study the effects of NO on development. A role was found for NO in neurite growth and synaptic re-modelling after injury but this may not be entirely due to NO acting via cGMP and PKG. Nitric oxide regulates embryonic development and affects locomotion, heartbeat and feeding. Researchers found that in the buccal ganglion NO may act both synaptically and non-synaptically in neuronal communication [189–191]. Group 14 chose Helisoma trivolvis (pond snail), another aquatic snail, for their research. Rehder in particular investigated growth cone function extensively using this system. Nitric oxide significantly affects growth cone filopodial pathfinding and appears to act as a chemotactic agent itself. This response involves the standard sGC-cGMP-PKG pathway including an increase in intracellular calcium from intracellular sources. Additionally NO acting as a 3-D volume transmitter affects neurons via apamin-sensitive potassium channels. Nitric oxide also produced ADP-ribosylation and affected ciliary function in the embryo [122,192–201]. Finally group 15 used the marine mollusc Ilyanassa obsolete; Gifondorwa and Leise demonstrate NO is involved in both metamorphosis and apoptosis in this animal [202,203].
9. Molluscan physiology (Groups 16–20)

The next 5 groups summarize the direct effects of NO on neurons and nervous systems of selected molluscs. In this section there are sufficient numbers of significant publications to separate the species even more than for development; accordingly group 16 only covers land snails while pond and marine snails are covered subsequently in separate groups (Helix pomatia, Cepaea nemoralis, Helix lucorum, Helix aspersa, Megalobulimus abbreviates). The range of NO related research is quite extensive with publications ranging from NO interacting with peptidergic transmission (FMRFamide and GSPYFVamide) to the relationship between iron metabolism and NO to the effect of magnetic fields on opioid analgesia in which NO is implicated. Again NO is implicated in the response to hypoxia, cold and nociception. It affects the type of response to glutamate on N-methyl-D-aspartate (NMDA) receptors. Additionally NO is implicated as a secondary messenger for serotonin or even a co-transmitter and may act as a retrograde transmitter as well. Nitric oxide-generated cGMP can modulate the effect of an eicosanoid on cholinergic receptor function; it decreases an inward depolarizing current. Behaviorally NO is implicated in olfaction, memory formation, rest versus activity and the withdrawal reflex. Both PKA and PKG are probably involved in olfactory behavior in the procerebrum. Finally, as mentioned previously, the author performed his PhD thesis on Helix aspersa and this was aided immensely by the extensive mapping paper published by Kerkut et al. in the mid-seventies [204]. Unlike mammalian nervous systems, the simplicity and peripheral arrangement of large bodied neurons in molluscan nervous systems facilitates the production of such a resource and apart from being able to identify a particular neuron by its position and size, one now knew the pharmacological profile of that neuron which could confirm identity. The author used F1 which was a large, easily identifiable neuron to firstly confirm that NO could be produced endogenously and then, using NO-donors, to observe any direct effect on membrane potential. Diaphorase histochemistry and immunocytochemistry had previously demonstrated the presence of NOS in the nervous system of Helix aspersa [205,206]. The author confirmed the ability of neurons near to F1, and possibly F1 itself, to produce NO caused by acetylcholine-induced depolarization resulting in calcium entry and subsequent stimulation of NOS using the fluorescent NO reporter 4-amino-5-methylamino-2',7'-difluorofluorescein (DAF-FM). The author then went on to show NO and membrane-permeable cGMP appeared to have a direct hyperpolarizing effect on F1 and might interact with dopamine-induced hyperpolarization. This is interesting when one compares to results obtained from Helix pomatia where the NO-cGMP system appears to decrease a calcium-activated potassium current so increasing excitability. As in many insect papers previously discussed, the 3-D volume effect was cited as particularly important for NO’s functions in these animals’ nervous systems [207–227]. Group 17 used the land gastropod Limax (L. maximus, L. valentianus, L. marginatus) to investigate the effects of NO on neural tissue. In particular these animals have been used to investigate odor processing in the procerebrum with researchers such as Watanabe and Gelperin demonstrating the importance of NO in this function. The NO-cGMP system is thought to be involved in synchronizing system oscillations necessary for discrimination and learning and memory [228–235]. Group 18 focused on the pond snails Lymnaea stagnalis, Helisoma trivolvis and Planorbarius corneus as model animals. Feeding behavior was studied in this group and NO-cGMP are strongly implicated as they are in certain types of learning and memory and conditioning. Additionally the buccal ganglion, which regulates gut motility, is modulated by NO; rhythmic activity of these neurons is affected. Again NO is implicated in the
response to hypoxia and linked to iron metabolism. Nitric oxide appears to modulate serotoninergic synaptic transmission and may be a co-transmitter; again researchers linking effects specifically to NO’s ability to act in a 3-D manner due to being a hydrophobic gas. Nitric oxide can also affect the nature of the neuronal response to glutamate and the NO-sGC-PKG pathway and ADP ribosylation can release calcium from internal stores. Nitric oxide was implicated in the regulation of neuronal excitability and the ability to fire action potentials. Finally and quite significantly, the invertebrate equivalent of microglial cells respond to bacterial lipopolysaccharides by expressing iNOS similarly to mammals [215,226,236–258]. The next group (19) used the predatory sea snail Stramonita haemastoma and looked at the ability of the CNS to produce NO via NOS expression. Expression was particularly associated with sensory afferents plus it was discovered NO is probably involved in the response to environmental stress [259,260]. Group 20 includes the bivalve molluscs Crenomytilus grayanus, Mytilus edulis and Pecten irradians. As it might be expected with such filter feeders, they have been utilized for studies on neuroprotection from pollution, temperature stress and hypoxia in which NO has been implicated. Most interestingly though may be the utilization of Mytilus for transcutaneous electrical nerve stimulation (TENS) research; similarly to the system found in mammals, TENS causes NO production via opiate signaling which is related to a subject currently causing great social concern. In addition NO appears to be involved in regulating gill filament ciliary activity; dopaminergic inhibition is antagonized by endogenous opioids acting via novel receptors and whose effect is mimicked by NO donors [261–266].

10. Aplysia and other sea slugs (Group 21)

Although molluscs, the sea slugs/hares deserve their own group as becomes their principal genus Aplysia as the invertebrate model used extensively for research into conditioned reflexes and learning and memory by such luminaries as Eric Kandel. Pleurobranchaea californica and Onchidium are also included in this group. Applying a filter to this group to just consider significant NO publications still reveals a wide range of important topics. Again NO appears involved in some forms of feeding and this can be localized to some extent to the buccal ganglion. Specifically NO is involved in swallowing and may even function in memory formation concerning swallowing. Nitric oxide is also implicated in preparing for egg laying. Nitric oxide possibly produced by interneurons can affect synaptic transmission, especially between sensory neurons and motorneurons; chemosensory areas of the mouth show NOS expression. Additionally it appears histamine and NO are likely co-transmitters. Sung et al. looked at the phenomenon of long-term hyperexcitability induced by axotomy which involves the NO-sGC-PKG pathway. This could potentially be a model for studying neuropathic pain targets. This group in particular is also a treasure trove of direct effects of NO on neurons. Nitric oxide apparently can inhibit or enhance inward depolarizing Na⁺ currents and potentiates a cAMP-mediated cation current. Nitric oxide also affects acetylcholine-(K⁺), dopamine-(K⁺), met-enkephalin-(K⁺) and glutamate-induced (Cl⁻) hyperpolarizing currents principally via cGMP. It was found that NO can also modulate acetylcholine release at synapses [267–289].
11. Crustacean development (Group 22)

This group involves development studies using the lobster Homarus americanus. In this animal NO is involved in development, especially of the olfactory system and in its response to injury. At hatching expression of NOS and sGC was particularly noticeable in the olfactory system and many neurons responded to NO by increasing cGMP production suggesting the standard NO-cGMP pathway. Interestingly neurons in the stomatogastric ganglion become responsive to NO at metamorphosis during which the nervous system is completely re-organized. Elevated cGMP was also observed in the cell nuclei possibly suggesting a role in transcription [290,291].

12. Crustacean physiology (Groups 23 to 26)

These final groups bring together research on the physiological effects of NO on various selected crustaceans including the lobster Homarus americanus, Pacifastacus leniusculus (crayfish), Calanus finmarchicus (zooplankton) and various crabs including Cancer productus, Neohelice granulata, Hemigrapsus sanguineus and Cancer pagurus. In the lobster (group 23) NO appears involved in feedback in neuropeptide control of the heart whereby NO released by heart tissue affects neurons in the cardiac ganglion possibly in a retrograde manner [292–295]. In various crabs (group 24) pigment dispersal in the retina appears to depend on NO. Nitric oxide is also implicated in processing nociceptive stimuli and the so-called gastric mill in the stomatogastric ganglion’s spontaneous activity is significantly affected by NO. It should be noted that a membrane-located GC was found in this ganglion [296–301]. In crayfish (group 25) NO appears to be involved in glial cell apoptosis induced by photodynamic therapy (PDT) which is used in cancer treatment. Again NO is implicated in sensory perception, especially if plasticity is involved. Additionally NO and cAMP are involved in regulating swimmeret motorneurons and NO is implicated as a retrograde transmitter at NMJ’s where it appears to act presynaptically. For all these actions the standard NO-sCG-cGMP pathway appears to be the principal mechanism [302–313]. Finally there has even been some published research to suggest functions of the various gaseous transmitters (NO, CO and H2S) in zooplankton (group 26) [314]. After this brief survey the final section of this review will attempt to discuss some of the more important common functions of NO in these wonderful and intriguing animals.

13. What these wonderful animals have taught us about nitric oxide

Some of the obvious advantages to using invertebrate models such as those listed here have already been mentioned. Accessibility, size, relative simplicity and economy are all worth considering when compared to mammalian models especially when many basic neuronal phenomena appear to have common or similar mechanisms. For the vast majority of NO’s actions the same basic pathway of NO acting on sGC to produce the secondary messenger cGMP and acting on targets typified by PKG appears to be the common mechanism. However ADP-ribosylation should not be ignored as a potential means to affect the function of many proteins. Additionally, in many of these organisms NO has been strongly implicated as a retrograde synaptic transmitter. For development affected by NO in insects (groups 1–4) these model organisms have enabled us to video and directly observe neuronal development, including that of the behaviorally significant central complex. Nitric oxide is implicated in embryogenesis, neurogenesis and synaptogenesis. Development in molluscs
(groups 13–15) appears similarly affected by NO. Again embryogenesis and metamorphosis are affected together with cellular-level events such as neurite growth and apoptosis. Here, as in many areas, the fact that NO is a gas and can act 3-D volume transmitter appears crucial to its function. As for development in crustaceans (group 22), lobsters also need NO for metamorphosis and development of the olfactory system. Summarizing NO’s physiological actions on neurons, in insects (groups 5–12) it is strongly implicated in associative learning and in various stages of memory formation as well as regulating heart function. Nitric oxide is also implicated in sensory function, in particular olfactory discrimination; again NO acting as a 3-D volume transmitter appears crucial to its function. Molluscan neurophysiology (groups 16–21) has demonstrated that NO is implicated in neuropeptide function, iron metabolism, responses to hypoxia, cold and nociception. Again it is implicated in olfaction and odor processing and some types of learning and memory. Finally in crustaceans (groups 23–26) NO can affect the heart and gut and is implicated in sensory perception and apoptosis. Hopefully this brief summary has helped illustrate how useful invertebrate model systems can be when examining the function of such a novel messenger molecule as NO.

Conflict of interest

The author declares no conflict of interest.

References

1. Ignarro LJ, Buga GM, Wood KS, et al. (1987) Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Natl Acad Sci USA 84: 9265–9269.
2. Moncada S, Palmer RM, Higgs EA (1991) Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacol Rev 43: 109–142.
3. Palmer RM, Ferrige AG, Moncada S (1987) Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327: 524–526.
4. Moroz LL (2000) On the origin and early evolution of neuronal nitric oxide signaling: A comparative analysis. In: Kalsner S, editor. Nitric Oxide and Free Radicals in Peripheral Neurotransmission. Boston, MA: Birkhäuser Boston, 1–34.
5. Moroz LL, Kohn AB (2007) On the comparative biology of Nitric Oxide (NO) synthetic pathways: Parallel evolution of NO–mediated signaling. Adv Exp Biol 1: 1–44.
6. Zumft WG (1993) The biological role of nitric oxide in bacteria. Arch Microbiol 160: 253–264.
7. Zumft WG (2005) Nitric oxide reductases of prokaryotes with emphasis on the respiratory, heme-copper oxidase type. J Inorg Biochem 99: 194–215.
8. Moroz LL (2015) Gaseous transmission across time and species. Am Zool 41: 304–320.
9. Moroz LL, Kohn AB (2011) Parallel evolution of nitric oxide signaling: Diversity of synthesis and memory pathways. Front Biosci (Landmark Ed) 16: 2008–2051.
10. Brandes JA, Doctor NZ, Cody GD, et al. (1998) Abiotic nitrogen reduction on the early Earth. Nature 395: 365–367.
11. Kasting JF (1992) Bolide impacts and the oxidation state of carbon in the Earth’s early atmosphere. Orig Life Evol Biosph 20: 199–231.
12. Martin RS, Mather TA, Pyle DM (2007) Volcanic emissions and the early Earth atmosphere. Geochim Cosmochim Ac 71: 3673–3685.
13. Nna Mvondo D, Navarro-Gonzalez R, McKay CP, et al. (2001) Production of nitrogen oxides by lightning and coronae discharges in simulated early Earth, Venus and Mars environments. *Adv Space Res* 27: 217–223.

14. Nna-Mvondo D, Navarro-Gonzalez R, Raulin F, et al. (2005) Nitrogen fixation by corona discharge on the early precambrian Earth. *Orig Life Evol Biosph* 35: 401–409.

15. Summers DP, Chang S (1993) Prebiotic ammonia from reduction of nitrite by iron (II) on the early Earth. *Nature* 365: 630–633.

16. Flores-Santana W, Switzer C, Ridnour LA, et al. (2009) Comparing the chemical biology of NO and HNO. *Arch Pharm Res* 32: 1139–1153.

17. Fukuto JM, Cho JY, Switzer CH (2000) Chapter 2-The chemical properties of Nitric Oxide and related nitrogen oxides. In: Ignarro LJ, editor. *Nitric Oxide*. San Diego: Academic Press, 23–40.

18. Gladwin MT, Schechter AN, Kim-Shapiro DB, et al. (2005) The emerging biology of the nitrite anion. *Nat Chem Biol* 1: 308–314.

19. Stamler JS, Singel DJ, Loscalzo J (1992) Biochemistry of nitric oxide and its redox-activated forms. *Science* 258: 1898–1902.

20. Lancaster Jr JR (1994) Simulation of the diffusion and reaction of endogenously produced nitric oxide. *Proc Natl Acad Sci USA* 91: 8137–8141.

21. Lancaster Jr JR (1996) Diffusion of free nitric oxide. *Methods Enzymol* 268: 31–50.

22. Lancaster Jr JR (1997) A tutorial on the diffusibility and reactivity of free nitric oxide. *Nitric Oxide* 1: 18–30.

23. Thomas DD, Liu X, Kantrow SP, et al. (2001) The biological lifetime of nitric oxide: Implications for the perivascular dynamics of NO and O2. *Proc Natl Acad Sci USA* 98: 355–360.

24. Wood J, Garthwaite J (1994) Models of the diffusional spread of nitric oxide: implications for neural nitric oxide signalling and its pharmacological properties. *Neuropharmacology* 33: 1235–1244.

25. Bryan NS, Rassaf T, Maloney RE, et al. (2004) Cellular targets and mechanisms of nitros(yl)ation: An insight into their nature and kinetics in vivo. *Proc Natl Acad Sci USA* 101: 4308–4313.

26. Nathan C (2004) The moving frontier in nitric oxide-dependent signaling. *Sci STKE* 2004: pe52.

27. Benamar A, Rolletschek H, Borisjuk L, et al. (2008) Nitrite-nitric oxide control of mitochondrial respiration at the frontier of anoxia. *Biochim Biophys Acta* 1777: 1268–1275.

28. Hendgen-Cotta UB, Merx MW, Shiva S, et al. (2008) Nitrite reductase activity of myoglobin regulates respiration and cellular viability in myocardial ischemia-reperfusion injury. *Proc Natl Acad Sci USA* 105: 10256–10261.

29. Hill BG, Darley-Usmar VM (2008) S–nitrosation and thiol switching in the mitochondrion: A new paradigm for cardioprotection in ischaemic preconditioning. *Biochem J* 412: e11–13.

30. Lopez-Lluch G, Irusta PM, Navas P, et al. (2008) Mitochondrial biogenesis and healthy aging. *Exp Gerontol* 43: 813–819.

31. Moncada S, Bolanos JP (2006) Nitric oxide, cell bioenergetics and neurodegeneration. *J Neurochem* 97: 1676–1689.

32. Navarro A (2008) Mitochondrial nitric oxide synthase and the regulation of heart rate. *Am J Hypertens* 21: 485.

33. Nisoli E, Falcone S, Tonello C, et al. (2004) Mitochondrial biogenesis by NO yields functionally active mitochondria in mammals. *Proc Natl Acad Sci USA* 101: 16507–16512.
34. Nisoli E, Tonello C, Cardile A, et al. (2005) Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. *Science* 310: 314–317.

35. Quintero M, Colombo SL, Godfrey A, et al. (2006) Mitochondria as signaling organelles in the vascular endothelium. *Proc Natl Acad Sci USA* 103: 5379–5384.

36. Valdez LB, Boveris A (2007) Mitochondrial nitric oxide synthase, a voltage-dependent enzyme, is responsible for nitric oxide diffusion to cytosol. *Front Biosci* 12: 1210–1219.

37. Abe S, Nakabayashi S, Murayama J, et al. (2010) Development of a novel fluorometric assay for nitric oxide utilizing sesamol and its application to analysis of nitric oxide-releasing drugs. *Luminescence* 25: 456–462.

38. Boudko DY, Cooper BY, Harvey WR, et al. (2002) High-resolution microanalysis of nitrite and nitrate in neuronal tissues by capillary electrophoresis with conductivity detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 774: 97–104.

39. Chang JYH, Chow LW, Dismuke WM, et al. (2017) Peptide-Functionalized Fluorescent Particles for In Situ Detection of Nitric Oxide via Peroxynitrite-Mediated Nitration. *Adv Healthc Mater* 6.

40. Cruz L, Moroz LL, Gillette R, et al. (1997) Nitrite and nitrate levels in individual molluscan neurons: Single-cell capillary electrophoresis analysis. *J Neurochem* 69: 110–115.

41. Davies IR, Zhang X (2008) Nitric oxide selective electrodes. *Methods Enzymol* 436: 63–95.

42. Fuller RR, Moroz LL, Gillette R, et al. (1998) Single neuron analysis by capillary electrophoresis with fluorescence spectroscopy. *Neuron* 20: 173–181.

43. Ghafourifar P, Parihar MS, Nazarewicz R, et al. (2008) Detection assays for determination of mitochondrial nitric oxide synthase activity; advantages and limitations. *Methods Enzymol* 440: 317–334.

44. Ha Y, Sim J, Lee Y, et al. (2016) Insertable fast-response amperometric NO/CO dual microsensor: Study of neurovascular coupling during acutely induced seizures of rat brain cortex. *Anal Chem* 88: 2563–2569.

45. Li H, Wan A (2015) Fluorescent probes for real–time measurement of nitric oxide in living cells. *Analyst* 140: 7129–7141.

46. Likhtenshtein GI (2009) Novel fluorescent methods for biotechnological and biomedical sensing: Assessing antioxidants, reactive radicals, NO dynamics, immunoassay, and biomembranes fluidity. *Appl Biochem Biotechnol* 152: 135–155.

47. Moroz LL, Dahlgren RL, Boudko D, et al. (2005) Direct single cell determination of nitric oxide synthase related metabolites in identified nitrergic neurons. *J Inorg Biochem* 99: 929–939.

48. Moroz LL, Gillette R, Sweedler JV (1999) Single-cell analyses of nitrergic neurons in simple nervous systems. *J Exp Biol* 202: 333–341.

49. Moroz LL, Radbourne S, Winlow W (1995) The use of NO-sensitive microelectrodes for direct detection of nitric oxide (NO) production in molluscs. *Acta Biol Hung* 46: 155–167.

50. Nagano T (1999) Practical methods for detection of nitric oxide. *Luminescence* 14: 283–290.

51. Nagano T (2009) Bioimaging probes for reactive oxygen species and reactive nitrogen species. *J Clin Biochem Nutr* 45: 111–124.

52. Teng X, Scott Isbell T, Crawford JH, et al. (2008) Novel method for measuring S–nitrosothiols using hydrogen sulfide. *Methods Enzymol* 441: 161–172.

53. Vanin A, Poltorakov A (2009) NO spin trapping in biological systems. *Front Biosci (Landmark Ed)* 14: 4427–4435.
54. Ye X, Rubakhin SS, Sweedler JV (2008) Detection of nitric oxide in single cells. Analyst 133: 423–433.
55. Zhou X, He P (2011) Improved measurements of intracellular nitric oxide in intact microvessels using 4,5-diaminofluorescein diacetate. Am J Physiol Heart Circ Physiol 301: H108–114.
56. Elofsson R, Carlberg M, Moroz L, et al. (1993) Is nitric oxide (NO) produced by invertebrate neurones? Neuroreport 4: 279–282.
57. Lukowiak K, Moroz LL, Bulloch AGM, et al. (1993) Putative NO-synthesizing neurons of lymnaea in vivo and in vitro. Neth J Zool 44: 535–549.
58. Moroz LL (2000) Giant identified NO-releasing neurons and comparative histochemistry of putative nitrergic systems in gastropod molluscs. Microsc Res Tech 49: 557–569.
59. Moroz LL, Gillette R (1995) From polyplacophora to cephalopoda: Comparative analysis of nitric oxide signalling in mollusca. Acta Biol Hung 46: 169–182.
60. Bredt DS, Hwang PM, Snyder SH (1990) Localization of nitric oxide synthase indicating a neural role for nitric oxide. Nature 347: 768–770.
61. Bredt DS, Snyder SH (1990) Isolation of nitric oxide synthetase, a calmodulin-requiring enzyme. Proc Natl Acad Sci USA 87: 682–685.
62. Ghosh DK, Salerno JC (2003) Nitric oxide synthases: Domain structure and alignment in enzyme function and control. Front Biosci 8: d193–209.
63. Griffith OW, Stuehr DJ (1995) Nitric oxide synthases: Properties and catalytic mechanism. Annu Rev Physiol 57: 707–736.
64. Zemojtel T, Wade RC, Dandekar T (2003) In search of the prototype of nitric oxide synthase. FEBS Lett 554: 1–5.
65. Angelo M, Hausladen A, Singel DJ, et al. (2008) Interactions of NO with hemoglobin: From microbes to man. Methods Enzymol 436: 131–168.
66. Basu S, Azarova NA, Font MD, et al. (2008) Nitrite reductase activity of cytochrome c. J Biol Chem 283: 32590–32597.
67. Cosby K, Partovi KS, Crawford JH, et al. (2003) Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. Nat Med 9: 1498–1505.
68. Huang Z, Shiva S, Kim-Shapiro DB, et al. (2005) Enzymatic function of hemoglobin as a nitrite reductase that produces NO under allosteric control. J Clin Invest 115: 2099–2107.
69. Kollau A, Beretta M, Russwurm M, et al. (2009) Mitochondrial nitrite reduction coupled to soluble guanylate cyclase activation: Lack of evidence for a role in the bioactivation of nitroglycerin. Nitric Oxide 20: 53–60.
70. Noh H, Staniek K, Kozlov AV (2005) The existence and significance of a mitochondrial nitrite reductase. Redox Rep 10: 281–286.
71. Philippot L (2002) Denitrifying genes in bacterial and Archaeal genomes. Biochim Biophys Acta 1577: 355–376.
72. Reutov VP (2002) Nitric oxide cycle in mammals and the cyclicity principle. Biochemistry (Mosc) 67: 293–311.
73. Shiva S, Huang Z, Grubina R, et al. (2007) Deoxymyoglobin is a nitrite reductase that generates nitric oxide and regulates mitochondrial respiration. Circ Res 100: 654–661.
74. Bredt DS, Hwang PM, Glatt CE, et al. (1991) Cloned and expressed nitric oxide synthase structurally resembles cytochrome P-450 reductase. Nature 351: 714–718.
75. Lowenstein CJ, Glatt CS, Bredt DS, et al. (1992) Cloned and expressed macrophage nitric oxide synthase contrasts with the brain enzyme. *Proc Natl Acad Sci USA* 89: 6711–6715.
76. Lyons CR, Orloff GJ, Cunningham JM (1992) Molecular cloning and functional expression of an inducible nitric oxide synthase from a murine macrophage cell line. *J Biol Chem* 267: 6370–6374.
77. Xie QW, Cho HJ, Calaycay J, et al. (1992) Cloning and characterization of inducible nitric oxide synthase from mouse macrophages. *Science* 256: 225–228.
78. Janssens SP, Shimouchi A, Quertermous T, et al. (1992) Cloning and expression of a cDNA encoding human endothelium-derived relaxing factor/nitric oxide synthase. *J Biol Chem* 267: 14519–14522.
79. Lamas S, Marsden PA, Li GK, et al. (1992) Endothelial nitric oxide synthase: Molecular cloning and characterization of a distinct constitutive enzyme isoform. *Proc Natl Acad Sci USA* 89: 6348–6352.
80. Marsden PA, Schappert KT, Chen HS, et al. (1992) Molecular cloning and characterization of human endothelial nitric oxide synthase. *FEBS Lett* 307: 287–293.
81. Nishida K, Harrison DG, Navas JP, et al. (1992) Molecular cloning and characterization of the constitutive bovine aortic endothelial cell nitric oxide synthase. *J Clin Invest* 90: 2092–2096.
82. Sessa WC, Harrison JK, Barber CM, et al. (1992) Molecular cloning and expression of a cDNA encoding endothelial cell nitric oxide synthase. *J Biol Chem* 267: 15274–15276.
83. Knowles RG, Moncada S (1994) Nitric oxide synthases in mammals. *Biochem J* 298 (Pt 2): 249–258.
84. Zhou L, Zhu DY (2009) Neuronal nitric oxide synthase: Structure, subcellular localization, regulation, and clinical implications. *Nitric Oxide* 20: 223–230.
85. Radomski MW, Martin JF, Moncada S (1991) Synthesis of Nitric Oxide by the haemocytes of the American horseshoe crab (Limulus polyphemus). *Philos T R Soc B* 334: 129–133.
86. Garthwaite J (2019) NO as a multimodal transmitter in the brain: Discovery and current status. *Br J Pharmacol* 176: 197–211.
87. Russwurm M, Wittau N, Koesling D (2001) Guanylyl cyclase/PSD-95 interaction: Targeting of the nitric oxide-sensitive alpha2beta1 guanylyl cyclase to synaptic membranes. *J Biol Chem* 276: 44647–44652.
88. Schulz S, Chinkers M, Garbers DL (1989) The guanylate cyclase/receptor family of proteins. *Faseb J* 3: 2026–2035.
89. Arnold WP, Mittal CK, Katsuki S, et al. (1977) Nitric oxide activates guanylate cyclase and increases guanosine 3',5'-cyclic monophosphate levels in various tissue preparations. *Proc Natl Acad Sci USA* 74: 3203–3207.
90. Francis SH, Busch JL, Corbin JD, et al. (2010) cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. *Pharmacol Rev* 62: 525–563.
91. Foster MW, Hess DT, Stamler JS (2009) Protein S-nitrosylation in health and disease: A current perspective. *Trends Mol Med* 15: 391–404.
92. Hara MR, Agrawal N, Kim SF, et al. (2005) S-nitrosylated GAPDH initiates apoptotic cell death by nuclear translocation following Siah1 binding. *Nat Cell Biol* 7: 665–674.
93. Hess DT, Matsumoto A, Kim SO, et al. (2005) Protein S-nitrosylation: Purview and parameters. *Nat Rev Mol Cell Biol* 6: 150–166.
94. Kim WK, Choi YB, Rayudu PV, et al. (1999) Attenuation of NMDA receptor activity and neurotoxicity by nitroxy anion, NO. *Neuron* 24: 461–469.

95. Lipton SA, Choi YB, Pan ZH, et al. (1993) A redox-based mechanism for the neuroprotective and neurodestructive effects of nitric oxide and related nitroso-compounds. *Nature* 364: 626–632.

96. Lipton SA, Choi YB, Takahashi H, et al. (2002) Cysteine regulation of protein function—as exemplified by NMDA-receptor modulation. *Trends Neurosci* 25: 474–480.

97. Mannick JB, Hausladen A, Liu L, et al. (1999) Fas-induced caspase denitrosylation. *Science* 284: 651–654.

98. Sen N, Hara MR, Ahmad AS, et al. (2009) GOSPEL: A neuroprotective protein that binds to GAPDH upon S-nitrosylation. *Neuron* 63: 81–91.

99. Uehara T, Nakamura T, Yao D, et al. (2006) S-nitrosylated protein-disulphide isomerase links protein misfolding to neurodegeneration. *Nature* 441: 513–517.

100. Ball EE, Truman JW (1998) Developing grasshopper neurons show variable levels of guanylyl cyclase activity on arrival at their targets. *J Comp Neurol* 394: 1–13.

101. Haase A, Bicker G (2003) Nitric oxide and cyclic nucleotides are regulators of neuronal migration in an insect embryo. *Development* 130: 3977–3987.

102. Herbert Z, Rauser S, Williams L, et al. (2010) Developmental expression of neuromodulators in the central complex of the grasshopper Schistocerca gregaria. *J Morphol* 271: 1509–1526.

103. Knipp S, Bicker G (2009) A developmental study of enteric neuron migration in the grasshopper using immunological probes. *Dev Dyn* 238: 2837–2849.

104. Knipp S, Bicker G (2009) Regulation of enteric neuron migration by the gaseous messenger molecules CO and NO. *Development* 136: 85–93.

105. Seidel C, Bicker G (2000) Nitric oxide and cGMP influence axogenesis of antennal pioneer neurons. *Development* 127: 4541–4549.

106. Seidel C, Bicker G (2002) Developmental expression of nitric oxide/cyclic GMP signaling pathways in the brain of the embryonic grasshopper. *Brain Res Dev Brain Res* 138: 71–79.

107. Stern M, Bicker G (2008) Nitric oxide regulates axonal regeneration in an insect embryonic CNS. *Dev Neurobiol* 68: 295–308.

108. Stern M, Bicker G (2010) Nitric oxide as a regulator of neuronal motility and regeneration in the locust embryo. *J Insect Physiol* 56: 958–965.

109. Stern M, Boger N, Eickhoff R, et al. (2010) Development of nitrergic neurons in the nervous system of the locust embryo. *J Comp Neurol* 518: 1157–1175.

110. Truman JW, De Vente J, Ball EE (1996) Nitric oxide-sensitive guanylate cyclase activity is associated with the maturational phase of neuronal development in insects. *Development* 122: 3949–3958.

111. Enikolopov G, Banerji J, Kuzin B (1999) Nitric oxide and Drosophila development. *Cell Death Differ* 6: 956–963.

112. Gibbs SM, Becker A, Hardy RW, et al. (2001) Soluble guanylate cyclase is required during development for visual system function in Drosophila. *J Neurosci* 21: 7705–7714.

113. Gibbs SM, Truman JW (1998) Nitric oxide and cyclic GMP regulate retinal patterning in the optic lobe of Drosophila. *Neuron* 20: 83–93.

114. Kanao T, Sawada T, Davies SA, et al. (2012) The nitric oxide-cyclic GMP pathway regulates FoxO and alters dopaminergic neuron survival in Drosophila. *PLoS One* 7: e30958.
115. Kuzin B, Regulski M, Stasiv Y, et al. (2000) Nitric oxide interacts with the retinoblastoma pathway to control eye development in Drosophila. *Curr Biol* 10: 459–462.

116. Kuzin B, Roberts I, Peunova N, et al. (1996) Nitric oxide regulates cell proliferation during Drosophila development. *Cell* 87: 639–649.

117. Lacin H, Rusch J, Yeh RT, et al. (2014) Genome-wide identification of Drosophila Hb9 targets reveals a pivotal role in directing the transcriptome within eight neuronal lineages, including activation of nitric oxide synthase and Fd59a/Fox-D. *Dev Biol* 388: 117–133.

118. Rabinovich D, Yaniv SP, Alyagor I, et al. (2016) Nitric Oxide as a switching mechanism between axon degeneration and regrowth during developmental remodeling. *Cell* 164: 170–182.

119. Regulski M, Stasiv Y, Tully T, et al. (2004) Essential function of nitric oxide synthase in Drosophila. *Curr Biol* 14: R881–882.

120. Regulski M, Tully T (1995) Molecular and biochemical characterization of dNOS: A Drosophila Ca2+/calmodulin-dependent nitric oxide synthase. *Proc Natl Acad Sci USA* 92: 9072–9076.

121. Shakiryanova D, Levitan ES (2008) Prolonged presynaptic posttetanic cyclic GMP signaling in Drosophila motoneurons. *Proc Natl Acad Sci USA* 105: 13610–13613.

122. Van Wagener S, Rehder V (1999) Regulation of neuronal growth cone filopodia by nitric oxide. *J Neurobiol* 39: 168–185.

123. Wildemann B, Bicker G (1999) Developmental expression of nitric oxide/cyclic GMP synthesizing cells in the nervous system of Drosophila melanogaster. *J Neurobiol* 38: 1–15.

124. Wingrove JA, O'Farrell PH (1999) Nitric oxide contributes to behavioral, cellular, and developmental responses to low oxygen in Drosophila. *Cell* 98: 105–114.

125. Champlin DT, Truman JW (2000) Ecdysteroid coordinates optic lobe neurogenesis via a nitric oxide signaling pathway. *Development* 127: 3543–3551.

126. Gibson NJ, Nighorn A (2000) Expression of nitric oxide synthase and soluble guanylyl cyclase in the developing olfactory system of Manduca sexta. *J Comp Neurol* 422: 191–205.

127. Gibson NJ, Rossler W, Nighorn AJ, et al. (2001) Neuron-glia communication via nitric oxide is essential in establishing antennal-lobe structure in Manduca sexta. *Dev Biol* 240: 326–339.

128. Grueber WB, Truman JW (1999) Development and organization of a nitric-oxide-sensitive peripheral neural plexus in larvae of the moth, Manduca sexta. *J Comp Neurol* 404: 127–141.

129. Qazi S, Trimmer BA (1999) The role of nitric oxide in motoneuron spike activity and muscarinic-evoked changes in cGMP in the CNS of larval Manduca sexta. *J Comp Physiol A* 185: 539–550.

130. Schachtner J, Homberg U, Truman JW (1999) Regulation of cyclic GMP elevation in the developing antennal lobe of the Sphinx moth, Manduca sexta. *J Neurobiol* 41: 359–375.

131. Wright JW, Schwinof KM, Snyder MA, et al. (1998) A delayed role for nitric oxide-sensitive guanylate cyclases in a migratory population of embryonic neurons. *Dev Biol* 204: 15–33.

132. Zayas RM, Qazi S, Morton DB, et al. (2000) Neurons involved in nitric oxide-mediated cGMP signaling in the tobacco hornworm, Manduca sexta. *J Comp Neurol* 419: 422–438.

133. Cayre M, Malaterre J, Scotto-Lomassese S, et al. (2005) A role for nitric oxide in sensory-induced neurogenesis in an adult insect brain. *Eur J Neurosci* 21: 2893–2902.

134. Bicker G (1996) Transmitter-induced calcium signalling in cultured neurons of the insect brain. *J Neurosci Methods* 69: 33–41.
135. Dacher M, Gauthier M (2008) Involvement of NO-synthase and nicotinic receptors in learning in the honey bee. *Physiol Behav* 95: 200–207.

136. Hosler JS, Buxton KL, Smith BH (2000) Impairment of olfactory discrimination by blockade of GABA and nitric oxide activity in the honey bee antennal lobes. *Behav Neurosci* 114: 514–525.

137. Menzel R, Muller U (1996) Learning and memory in honeybees: From behavior to neural substrates. *Annu Rev Neurosci* 19: 379–404.

138. Muller U, Hildebrandt H (2002) Nitric oxide/cGMP-mediated protein kinase A activation in the antennal lobes plays an important role in appetitive reflex habituation in the honeybee. *J Neurosci* 22: 8739–8747.

139. Muller U (1996) Inhibition of nitric oxide synthase impairs a distinct form of long-term memory in the honeybee, Apis mellifera. *Neuron* 16: 541–549.

140. Armstrong GA, Rodgers CI, Money TG, et al. (2009) Suppression of spreading depression-like events in locusts by inhibition of the NO/cGMP/PKG pathway. *J Neurosci* 29: 8225–8235.

141. Bicker G, Schmachtenberg O (1997) Cytochemical evidence for nitric oxide/cyclic GMP signal transmission in the visual system of the locust. *Eur J Neurosci* 9: 189–193.

142. Bullerjahn A, Mentel T, Pfluger HJ, et al. (2006) Nitric oxide: A co-modulator of efferent peptidergic neurosecretory cells including a unique octopaminergic neurone innervating locust heart. *Cell Tissue Res* 325: 345–360.

143. Homberg U (2002) Neurotransmitters and neuropeptides in the brain of the locust. *Microsc Res Tech* 56: 189–209.

144. Kurylas AE, Ott SR, Schachtner J, et al. (2005) Localization of nitric oxide synthase in the central complex and surrounding midbrain neuropils of the locust *Schistocerca gregaria*. *J Comp Neurol* 484: 206–223.

145. Muller U, Bicker G (1994) Calcium-activated release of nitric oxide and cellular distribution of nitric oxide-synthesizing neurons in the nervous system of the locust. *J Neurosci* 14: 7521–7528.

146. Munch D, Ott SR, Pfluger HJ (2010) Three-dimensional distribution of NO sources in a primary mechanosensory integration center in the locust and its implications for volume signaling. *J Comp Neurol* 518: 2903–2916.

147. Newland PL, Yates P (2008) Nitric oxide modulates salt and sugar responses via different signaling pathways. *Chem Senses* 33: 347–356.

148. Ott SR, Delago A, Elphick MR (2004) An evolutionarily conserved mechanism for sensitization of soluble guanylyl cyclase reveals extensive nitric oxide-mediated upregulation of cyclic GMP in insect brain. *Eur J Neurosci* 20: 1231–1244.

149. Ott SR, Jones IW, Burrows M, et al. (2000) Sensory afferents and motor neurons as targets for nitric oxide in the locust. *J Comp Neurol* 422: 521–532.

150. Ott SR, Philippides A, Elphick MR, et al. (2007) Enhanced fidelity of diffusive nitric oxide signalling by the spatial segregation of source and target neurones in the memory centre of an insect brain. *Eur J Neurosci* 25: 181–190.

151. Rast GF (2001) Nitric oxide induces centrally generated motor patterns in the locust suboesophageal ganglion. *J Exp Biol* 204: 3789–3801.

152. Schuppe H, Cuttle M, Newland PL (2007) Nitric oxide modulates sodium taste via a cGMP–independent pathway. *Dev Neurobiol* 67: 219–232.

153. Schuppe H, Newland PL (2011) Differential effects of nitric oxide on the responsiveness of tactile hairs. *Invert Neurosci* 11: 85–90.
154. Seidel C, Bicker G (1997) Colocalization of NADPH–diaphorase and GABA-immunoreactivity in the olfactory and visual system of the locust. *Brain Res* 769: 273–280.

155. Siegl T, Schachter J, Holstein GR, et al. (2009) NO/cGMP signalling: L-citrulline and cGMP immunostaining in the central complex of the desert locust *Schistocerca gregaria*. *Cell Tissue Res* 337: 327–340.

156. Collmann C, Carlsson MA, Hansson BS, et al. (2004) Odorant-evoked nitric oxide signals in the antennal lobe of *Manduca sexta*. *J Neurosci* 24: 6070–6077.

157. Gage SL, Daly KC, Nighorn A (2013) Nitric oxide affects short-term olfactory memory in the antennal lobe of *Manduca sexta*. *J Exp Biol* 216: 3294–3300.

158. Higgins M, Miller M, Nighorn A (2012) Nitric oxide has differential effects on currents in different subsets of *Manduca sexta* antennal lobe neurons. *PLoS One* 7: e42556.

159. Nighorn A, Gibson NJ, Rivers DM, et al. (1998) The nitric oxide-cGMP pathway may mediate communication between sensory afferents and projection neurons in the antennal lobe of *Manduca sexta*. *J Neurosci* 18: 7244–7255.

160. Seki Y, Aonuma H, Kanzaki R (2005) Pheromone processing center in the protocerebrum of *Bombyx mori* revealed by nitric oxide-induced anti-cGMP immunocytochemistry. *J Comp Neurol* 481: 340–351.

161. Simpson PJ, Nighorn A, Morton DB (1999) Identification of a novel guanylyl cyclase that is related to receptor guanylyl cyclases, but lacks extracellular and transmembrane domains. *J Biol Chem* 274: 4440–4446.

162. Wilson CH, Christensen TA, Nighorn AJ (2007) Inhibition of nitric oxide and soluble guanylyl cyclase signaling affects olfactory neuron activity in the moth, *Manduca sexta*. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 193: 715–728.

163. Zayas RM, Qazi S, Morton DB, et al. (2002) Nicotinic-acetylcholine receptors are functionally coupled to the nitric oxide/cGMP-pathway in insect neurons. *J Neurochem* 83: 421–431.

164. Zayas RM, Trimmer BA (2007) Characterization of NO/cGMP-mediated responses in identified motoneurons. *Cell Mol Neurobiol* 27: 191–209.

165. Duan J, Li W, Yuan D, et al. (2012) Nitric oxide signaling modulates cholinergic synaptic input to projection neurons in Drosophila antennal lobes. *Neuroscience* 219: 1–9.

166. Morton DB (2004) Atypical soluble guanylyl cyclases in *Drosophila* can function as molecular oxygen sensors. *J Biol Chem* 279: 50651–50653.

167. Ray SS, Sengupta R, Tiso M, et al. (2007) Reductase domain of Drosophila melanogaster nitric-oxide synthase: Redox transformations, regulation, and similarity to mammalian homologues. *Biochemistry* 46: 11865–11873.

168. Wildemann B, Bicker G (1999) Nitric oxide and cyclic GMP induce vesicle release at Drosophila neuromuscular junction. *J Neurobiol* 39: 337–346.

169. Greenfield MD (2001) Missing link in firefly bioluminescence revealed: NO regulation of photocye respiration. *Bioessays* 23: 992–995.

170. Murata Y, Mashiko M, Ozaki M, et al. (2004) Intrinsic nitric oxide regulates the taste response of the sugar receptor cell in the blowfly, *Phormia regina*. *Chem Senses* 29: 75–81.

171. Nakamura T, Murata Y, Mashiko M, et al. (2005) The nitric oxide–cyclic GMP cascade in sugar receptor cells of the blowfly, *Phormia regina*. *Chem Senses* 30 Suppl 1: i281–282.
172. Wasserman SL, Itagaki H (2003) The olfactory responses of the antenna and maxillary palp of the fleshfly, Neobellieria bullata (Diptera: Sarcophagidae), and their sensitivity to blockage of nitric oxide synthase. *J Insect Physiol* 49: 271–280.

173. Kunst M, Pförtner R, Aschenbrenner K, et al. (2011) Neurochemical architecture of the central complex related to its function in the control of grasshopper acoustic communication. *PLoS One* 6: e25613.

174. Weinrich A, Kunst M, Wirmer A, et al. (2008) Suppression of grasshopper sound production by nitric oxide-releasing neurons of the central complex. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 194: 763–776.

175. Wenzel B, Kunst M, Gunther C, et al. (2005) Nitric oxide/cyclic guanosine monophosphate signaling in the central complex of the grasshopper brain inhibits singing behavior. *J Comp Neurol* 488: 129–139.

176. Wirmer A, Heinrich R (2011) Nitric oxide/cGMP signaling in the corpora allata of female grasshoppers. *J Insect Physiol* 57: 94–107.

177. Muller U (2000) Prolonged activation of cAMP–dependent protein kinase during conditioning induces long-term memory in honeybees. *Neuron* 27: 159–168.

178. Aonuma H, Kitamura Y, Niwa K, et al. (2008) Nitric oxide-cyclic guanosine monophosphate signaling in the local circuit of the cricket abdominal nervous system. *Neuroscience* 157: 749–761.

179. Aonuma H, Niwa K (2004) Nitric oxide regulates the levels of cGMP accumulation in the cricket brain. *Acta Biol Hung* 55: 65–70.

180. Cayre M, Malaterre J, Scotto-Lomassese S, et al. (2005) Hormonal and sensory inputs regulate distinct neuroblast cell cycle properties in adult cricket brain. *J Neurosci Res* 82: 659–664.

181. Kosakai K, Tsujiuchi Y, Yoshino M (2015) Nitric oxide augments single Ca(2+) channel currents via cGMP-dependent protein kinase in Kenyon cells isolated from the mushroom body of the cricket brain. *J Insect Physiol* 78: 26–32.

182. Matsumoto Y, Hatano A, Unoki S, et al. (2009) Stimulation of the cAMP system by the nitric oxide-cGMP system underlying the formation of long-term memory in an insect. *Neurosci Lett* 467: 81–85.

183. Stevenson PA, Schildberger K (2013) Mechanisms of experience dependent control of aggression in crickets. *Curr Opin Neurobiol* 23: 318–323.

184. Mannai S, Bitri L, Than SH (2016) cGMP/cGMP-dependent protein kinase pathway modulates nicotine-induced currents through the activation of alpha-bungarotoxin-insensitive nicotinic acetylcholine receptors from insect neurosecretory cells. *J Neurochem* 137: 931–938.

185. Matsumoto CS, Kuramochi T, Matsumoto Y, et al. (2013) Participation of NO signaling in formation of long-term memory in salivary conditioning of the cockroach. *Neurosci Lett* 541: 4–8.

186. Nieto-Fernandez FE, Ianuzzi F, Ruiz A, et al. (2004) Estradiol-stimulated nitric oxide release in nervous tissue, vasculature, and gonads of the giant cockroach Blaberus craniifer. *Acta Biol Hung* 55: 143–148.

187. Ott SR, Elphick MR (2002) Nitric oxide synthase histochemistry in insect nervous systems: Methanol/formalin fixation reveals the neuroarchitecture of formaldehyde-sensitive NADPH diaphorase in the cockroach Periplaneta americana. *J Comp Neurol* 448: 165–185.
188. Wicher D, Messutat S, Lavialle C, et al. (2004) A new regulation of non-capacitative calcium entry in insect pacemaker neurosecretory neurons. Involvement of arachidonic acid, no-guanylyl cyclase/cGMP, and cAMP. *J Biol Chem* 279: 50410–50419.

189. Cooke RM, Mistry R, Challiss RA, et al. (2013) Nitric oxide synthesis and cGMP production is important for neurite growth and synapse remodeling after axotomy. *J Neurosci* 33: 5626–5637.

190. Park JH, Straub VA, O’Shea M (1998) Anterograde signaling by nitric oxide: Characterization and in vitro reconstitution of an identified nitrenergic synapse. *J Neurosci* 18: 5463–5476.

191. Serfozo Z, Elekes K (2002) Nitric oxide level regulates the embryonic development of the pond snail *Lymnaea stagnalis*: Pharmacological, behavioral, and ultrastructural studies. *Cell Tissue Res* 310: 119–130.

192. Artinian L, Tornieri K, Zhong L, et al. (2010) Nitric oxide acts as a volume transmitter to modulate electrical properties of spontaneously firing neurons via apamin-sensitive potassium channels. *J Neurosci* 30: 1699–1711.

193. Cole AG, Mashkournia A, Parries SC, et al. (2002) Regulation of early embryonic behavior by nitric oxide in the pond snail *Helisoma trivolvis*. *J Exp Biol* 205: 3143–3152.

194. Estes S, Artinian L, Rehder V (2017) Modulation of growth cone filopodial length by carbon monoxide. *Dev Neurobiol* 77: 677–690.

195. Estes S, Zhong LR, Artinian L, et al. (2015) The role of action potentials in determining neuron-type-specific responses to nitric oxide. *Dev Neurobiol* 75: 435–451.

196. Tornieri K, Rehder V (2007) Nitric oxide release from a single cell affects filopodial motility on growth cones of neighboring neurons. *Dev Neurobiol* 67: 1932–1943.

197. Trimm KR, Rehder V (2004) Nitric oxide acts as a slow-down and search signal in developing neurites. *Eur J Neurosci* 19: 809–818.

198. Van Wagenen S, Cheng S, Rehder V (1999) Stimulation-induced changes in filopodial dynamics determine the action radius of growth cones in the snail *Helisoma trivolvis*. *Cell Motil Cytoskeleton* 44: 248–262.

199. Van Wagenen S, Rehder V (2001) Regulation of neuronal growth cone filopodia by nitric oxide depends on soluble guanylyl cyclase. *J Neurobiol* 46: 206–219.

200. Welshhans K, Rehder V (2005) Local activation of the nitric oxide/cyclic guanosine monophosphate pathway in growth cones regulates filopodial length via protein kinase G, cyclic ADP ribose and intracellular Ca\(^{2+}\) release. *Eur J Neurosci* 22: 3006–3016.

201. Welshhans K, Rehder V (2007) Nitric oxide regulates growth cone filopodial dynamics via ryanodine receptor-mediated calcium release. *Eur J Neurosci* 26: 1537–1547.

202. Gifondorwa DJ, Leise EM (2006) Programmed cell death in the apical ganglion during larval metamorphosis of the marine mollusc *Ilyanassa obsoleta*. *Biol Bull* 210: 109–120.

203. Leise EM, Kempf SC, Durham NR, et al. (2004) Induction of metamorphosis in the marine gastropod *Ilyanassa obsoleta*: 5HT, NO and programmed cell death. *Acta Biol Hung* 55: 293–300.

204. Kerkut GA, Lambert JD, Gayton RJ, et al. (1975) Mapping of nerve cells in the suboesophageal ganglia of *Helix aspersa*. *Comp Biochem Physiol A Comp Physiol* 50: 1–25.

205. Pisu MB, Conforti E, Fenoglio C, et al. (1999) Nitric oxide-containing neurons in the nervous ganglia of *Helix aspersa* during rest and activity: Immunocytochemical and enzyme histochemical detection. *J Comp Neurol* 409: 274–284.
206. Sanchez-Alvarez M, Leon–Olea M, Talavera E, et al. (1994) Distribution of NADPH-diaphorase in the perioesophageal ganglia of the snail, Helix aspersa. Neurosci Lett 169: 51–55.

207. D’Yakonova TL (2000) NO-producing compounds transform neuron responses to glutamate. Neurosci Behav Physiol 30: 153–159.

208. D’Yakonova TL (2002) Interaction between serotonin and nitric oxide (NO) in the activation of the serotonergic system in the common snail. Neurosci Behav Physiol 32: 275–282.

209. D’Yakonova TL, Reutov VP (2000) The effects of nitrite on the excitability of brain neurons in the common snail. Neurosci Behav Physiol 30: 179–186.

210. Huang S, Kerschbaum HH, Hermann A (1998) Nitric oxide-mediated cGMP synthesis in Helix neural ganglia. Brain Res 780: 329–336.

211. Kavaliers M, Choleris E, Prato FS, et al. (1998) Evidence for the involvement of nitric oxide and nitric oxide synthase in the modulation of opioid-induced antinociception and the inhibitory effects of exposure to 60-Hz magnetic fields in the land snail. Brain Res 809: 50–57.

212. Kavaliers M, Prato FS (1999) Light-dependent effects of magnetic fields on nitric oxide activation in the land snail. Neuroreport 10: 1863–1867.

213. Korshunova TA, Balaban PM (2014) Nitric oxide is necessary for long-term facilitation of synaptic responses and for development of context memory in terrestrial snails. Neuroscience 266: 127–135.

214. Malyshev AY, Balaban PM (1999) Synaptic facilitation in Helix neurons depends upon postsynaptic calcium and nitric oxide. Neurosci Lett 261: 65–68.

215. Nacsa K, Elekes K, Serfozo Z (2015) Ultrastructural localization of NADPH diaphorase and nitric oxide synthase in the neuropils of the snail CNS. Micron 75: 58–66.

216. Pedder SM, Muneoka Y, Walker RJ (1998) Evidence for the involvement of nitric oxide in the inhibitory effect of GSPYFVamide on Helix aspersa central neurones. Regul Pept 74: 121–127.

217. Pivovarov AS, Egido-Villareal W (1996) NO synthase and guanylate cyclase inhibitors block modulation of the plasticity of common snail cholinoreceptors by 15-hydroxy-eicosatetraenoic acid. Neurosci Behav Physiol 26: 428–434.

218. Rigon P, de Castilhos J, Molina CG, et al. (2010) Distribution of NADPH-diaphorase activity in the central nervous system of the young and adult land snail Megalobulimus abbreviatus. Tissue Cell 42: 307–313.

219. Rigon P, de Castilhos J, Saur L, et al. (2009) NADPH-diaphorase activity in the nociceptive pathways of land snail Megalobulimus abbreviatus: The involvement of pedal ganglia. Invert Neurosci 9: 155–165.

220. Roszer T, Jenei Z, Gall T, et al. (2004) A possible stimulatory effect of FMRFamide on neural nitric oxide production in the central nervous system of Helix lucorum L. Brain Behav Evol 63: 23–33.

221. Roszer T, Kiss-Toth E, Rozsa D, et al. (2010) Hypothermia translocates nitric oxide synthase from cytosol to membrane in snail neurones. Cell Tissue Res 342: 191–203.

222. Schrofner S, Zsombok A, Hermann A, et al. (2004) Nitric oxide decreases a calcium-activated potassium current via activation of phosphodiesterase 2 in Helix U-cells. Brain Res 999: 98–105.

223. Serfozo Z, Nacsa K, Vereb Z, et al. (2017) Nitric oxide-coupled signaling in odor elicited molecular events in the olfactory center of the terrestrial snail, Helix pomatia. Cell Signal 30: 67–81.
224. Serfozo Z, Szentmiklosi AJ, Elekes K (2008) Characterization of nitric oxidergic neurons in the alimentary tract of the snail Helix pomatia L.: Histochemical and physiological study. *J Comp Neurol* 506: 801–821.

225. Wright NJ, Sides LJ, Walling K (2015) Initial studies on the direct and modulatory effects of nitric oxide on an identified central Helix aspersa neuron. *Invert Neurosci* 15: 175.

226. Xie M, Hermann A, Richter K, et al. (2001) Nitric oxide up-regulates ferritin mRNA level in snail neurons. *Eur J Neurosci* 13: 1479–1486.

227. Zsombok A, Schrofner S, Hermann A, et al. (2000) Nitric oxide increases excitability by depressing a calcium activated potassium current in snail neurons. *Neurosci Lett* 295: 85–88.

228. Fujie S, Yamamoto T, Murakami J, et al. (2005) Nitric oxide synthase and soluble guanylyl cyclase underlying the modulation of electrical oscillations in a central olfactory organ. *J Neurobiol* 62: 14–30.

229. Gelperin A (1994) Nitric oxide mediates network oscillations of olfactory interneurons in a terrestrial mollusc. *Nature* 369: 61–63.

230. Gelperin A, Flores J, Raccuia-Behling F, et al. (2000) Nitric oxide and carbon monoxide modulate oscillations of olfactory interneurons in a terrestrial mollusk. *J Neurophysiol* 83: 116–127.

231. Inoue T, Watanabe S, Kirino Y (2001) Serotonin and NO complementarily regulate generation of oscillatory activity in the olfactory CNS of a terrestrial mollusk. *J Neurophysiol* 85: 2634–2638.

232. Matsuo R, Ito E (2009) A novel nitric oxide synthase expressed specifically in the olfactory center. *Biochem Biophys Res Commun* 386: 724–728.

233. Watanabe S, Hirono M (2016) Phase-dependent modulation of oscillatory phase and synchrony by long-lasting depolarizing inputs in central neurons. *eNeuro* 3.

234. Watanabe S, Kirino Y, Gelperin A (2008) Neural and molecular mechanisms of microcognition in Limax. *Learn Mem* 15: 633–642.

235. Watanabe S, Takanashi F, Ishida K, et al. (2015) Nitric oxide-mediated modulation of central network dynamics during olfactory perception. *PLoS One* 10: e0136846.

236. Artinian L, Zhong L, Yang H, et al. (2012) Nitric oxide as intracellular modulator: Internal production of NO increases neuronal excitability via modulation of several ionic conductances. *Eur J Neurosci* 36: 3333–3343.

237. Dyakonova TL, Dyakonova VE (2008) Modification of the effects of glutamate by nitric oxide (NO) in a pattern-generating network. *Neurosci Behav Physiol* 38: 407–413.

238. Dyakonova TL, Dyakonova VE (2008) Electrical activity of no-producing neuron depends on NO level. *Bull Exp Biol Med* 145: 665–668.

239. Dyakonova VE, Dyakonova TL (2010) Coordination of rhythm-generating units via NO and extrasynaptic neurotransmitter release. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 196: 529–541.

240. Elliott CJ, Vehovszky A (2000) Comparative pharmacology of feeding in molluscs. *Acta Biol Hung* 51: 153–163.

241. Elphick MR, Kemenes G, Staras K, et al. (1995) Behavioral role for nitric oxide in chemosensory activation of feeding in a mollusc. *J Neurosci* 15: 7653–7664.
242. Erokhova LA, Brazhe NA, Maksimov GV, et al. (2005) Analysis of conformational changes in neuronal carotenoids under the influence of neuromediator. *Dokl Biochem Biophys* 402: 233–235.

243. Kobayashi S, Ogawa H, Fujito Y, et al. (2000) Nitric oxide suppresses fictive feeding response in *Lymnaea stagnalis*. *Neurosci Lett* 285: 209–212.

244. Kobayashi S, Sadamoto H, Ogawa H, et al. (2000) Nitric oxide generation around buccal ganglia accompanying feeding behavior in the pond snail, *Lymnaea stagnalis*. *Neurosci Res* 38: 27–34.

245. Korneev SA, Kemenes I, Straub V, et al. (2002) Suppression of nitric oxide (NO)-dependent behavior by double-stranded RNA-mediated silencing of a neuronal NO synthase gene. *J Neurosci* 22: Rc227.

246. Korneev SA, Straub V, Kemenes I, et al. (2005) Timed and targeted differential regulation of nitric oxide synthase (NOS) and anti-NOS genes by reward conditioning leading to long-term memory formation. *J Neurosci* 25: 1188–1192.

247. Lukowiak K, Martens K, Orr M, et al. (2006) Modulation of a cerebral respiratory behaviour in a pond snail. *Respir Physiol Neurobiol* 154: 61–72.

248. Moghadam HF, Winlow W, Moroz LL (1995) Effects of hydrogen peroxide and nitric oxide (NO) on neuronal discharges and intracellular calcium concentration in the molluscan CNS. *Acta Biol Hung* 46: 145–153.

249. Moroz LL, Park JH, Winlow W (1993) Nitric oxide activates buccal motor patterns in *Lymnaea stagnalis*. *Neuroreport* 4: 643–646.

250. Patel BA, Arundell M, Parker KH, et al. (2006) Detection of nitric oxide release from single neurons in the pond snail, *Lymnaea stagnalis*. *Anal Chem* 78: 7643–7648.

251. Peruzzi E, Fontana G, Sonetti D (2004) Presence and role of nitric oxide in the central nervous system of the freshwater snail *Planorbarius corneus*: Possible implication in neuron-microglia communication. *Brain Res* 1005: 9–20.

252. Ribeiro M, Straub VA, Schofield M, et al. (2008) Characterization of NO-sensitive guanylyl cyclase: Expression in an identified interneuron involved in NO-cGMP-dependent memory formation. *Eur J Neurosci* 28: 1157–1165.

253. Sidorov AV, Kazakevich VB, Moroz LL (1999) Nitric oxide selectively enhances cAMP levels and electrical coupling between identified RPAd2/VD1 neurons in the CNS of *Lymnaea stagnalis* (L.). *Acta Biol Hung* 50: 229–233.

254. Sonetti D, Ottaviani E, Stefano GB (1997) Opiate signaling regulates microglia activities in the invertebrate nervous system. *Gen Pharmacol* 29: 39–47.

255. Straub VA, Grant J, O’Shea M, et al. (2007) Modulation of serotonergic neurotransmission by nitric oxide. *J Neurophysiol* 97: 1088–1099.

256. Wyeth RC, Croll RP (2011) Peripheral sensory cells in the cephalic sensory organs of *Lymnaea stagnalis*. *J Comp Neurol* 519: 1894–1913.

257. Zhong LR, Estes S, Artinian L, et al. (2013) Nitric oxide regulates neuronal activity via calcium–activated potassium channels. *PLoS One* 8: e78727.

258. Zhong LR, Estes S, Artinian L, et al. (2015) Cell-specific regulation of neuronal activity by endogenous production of nitric oxide. *Eur J Neurosci* 41: 1013–1024.
259. Cioni C, Di Patti MC, Venturini G, et al. (2012) Cellular, biochemical, and molecular characterization of nitric oxide synthase expressed in the nervous system of the prosobranch Stramonita haemastoma (Gastropoda, Neogastropoda). J Comp Neurol 520: 364–383.

260. Toni M, De Angelis F, di Patti MC, et al. (2015) Nitric Oxide synthase in the central nervous system and peripheral organs of Stramonita haemastoma: Protein distribution and gene expression in response to thermal stress. Mar Drugs 13: 6636–6664.

261. Cadet P (2004) Nitric oxide modulates the physiological control of ciliary activity in the marine mussel Mytilus edulis via morphine: Novel mu opiate receptor splice variants. Neuro Endocrinol Lett 25: 184–190.

262. Cheng J, Zhang C, Han JS, et al. (2007) TENS stimulates constitutive nitric oxide release via opiate signaling in invertebrate neural tissues. Med Sci Monit 13: Br163–167.

263. Gomez MP, Nasi E (2000) Light transduction in invertebrate hyperpolarizing photoreceptors: Possible involvement of a Go-regulated guanylate cyclase. J Neurosci 20: 5254–5263.

264. Kotsyuba EP, Vaschenko MA (2010) Neuroplastic and neuropathological changes in the central nervous system of the Gray mussel Crenomytilus grayanus (Dunker) under environmental stress. Invert Neurosci 10: 35–46.

265. Stefano GB, Salzet B, Rialas CM, et al. (1997) Morphine- and anandamide-stimulated nitric oxide production inhibits presynaptic dopamine release. Brain Res 763: 63–68.

266. Vaschenko MA, Kotsyuba EP (2008) NADPH-diaphorase activity in the central nervous system of the Gray mussel Crenomytilus grayanus (Dunker) under stress conditions: A histochemical study. Mar Environ Res 66: 249–258.

267. Antonov I, Ha T, Antonova I, et al. (2007) Role of nitric oxide in classical conditioning of siphon withdrawal in Aplysia. J Neurosci 27: 10993–11002.

268. Hatcher NG, Sudlow LC, Moroz LL, et al. (2006) Nitric oxide potentiates cAMP-gated cation current in feeding neurons of Pleurobranchaea californica independent of cAMP and cGMP signaling pathways. J Neurophysiol 95: 3219–3227.

269. Jacklet JW, Tieman DG (2004) Nitric oxide and histamine induce neuronal excitability by blocking background currents in neuron MCC of Aplysia. J Neurophysiol 91: 656–665.

270. Katzoff A, Miller N, Susswein AJ (2010) Nitric oxide and histamine signal attempts to swallow: A component of learning that food is inedible in Aplysia. Learn Mem 17: 50–62.

271. Koh HY, Jacklet JW (1999) Nitric oxide stimulates cGMP production and mimics synaptic responses in metacerebral neurons of Aplysia. J Neurosci 19: 3818–3826.

272. Koh HY, Jacklet JW (2001) Nitric oxide induces cGMP immunoreactivity and modulates membrane conductance in identified central neurons of Aplysia. Eur J Neurosci 13: 553–560.

273. Lewin MR, Walters ET (1999) Cyclic GMP pathway is critical for inducing long-term sensitization of nociceptive sensory neurons. Nat Neurosci 2: 18–23.

274. Meulemans A, Mothet JP, Schirar A, et al. (1995) A nitric oxide synthase activity is involved in the modulation of acetylcholine release in Aplysia ganglion neurons: A histological, voltammetric and electrophysiological study. Neuroscience 69: 985–995.

275. Miller N, Katzoff A, Susswein AJ (2008) Nitric oxide induces aspects of egg-laying behavior in Aplysia. J Exp Biol 211: 2388–2396.

276. Miller N, Saada R, Fishman S, et al. (2011) Neurons controlling Aplysia feeding inhibit themselves by continuous NO production. PLoS One 6: e17779.
277. Moroz LL (2006) Localization of putative nitrergic neurons in peripheral chemosensory areas and the central nervous system of Aplysia californica. *J Comp Neurol* 495: 10–20.
278. Moroz LL, Chen D, Gillette MU, et al. (1996) Nitric oxide synthase activity in the molluscan CNS. *J Neurochem* 66: 873–876.
279. Mothet JP, Fossier P, Tauc L, et al. (1996) Opposite actions of nitric oxide on cholinergic synapses: Which pathways? *Proc Natl Acad Sci USA* 93: 8721–8726.
280. Potgieter K, Hatcher NG, Gillette R, et al. (2010) Nitric oxide potentiates cAMP-gated cation current by intracellular acidification in feeding neurons of pleurobranchaea. *J Neurophysiol* 104: 742–745.
281. Sawada M, Ichinose M (1996) Nitric oxide donor sodium nitroprusside inhibits the acetylcholine-induced K+ current in identified Aplysia neurons. *J Neurosci Res* 44: 21–26.
282. Sawada M, Ichinose M, Anraku M (1998) Nitric oxide donors inhibit the acetylcholine-induced Cl– current in identified Onchidium neurons. *J Neurobiol* 35: 388–394.
283. Sawada M, Ichinose M, Anraku M (2000) Inhibition of the glutamate-induced K(+) current in identified Onchidium neurons by nitric oxide donors. *J Neurosci Res* 60: 642–648.
284. Sawada M, Ichinose M, Hara N (1995) Nitric oxide induces an increased Na+ conductance in identified neurons of Aplysia. *Brain Res* 670: 248–256.
285. Sawada M, Ichinose M, Stefano GB (1996) Inhibition of the Met-enkephalin-induced K+ current in B-cluster neurons of Aplysia by nitric oxide donor. *Brain Res* 740: 124–130.
286. Sawada M, Ichinose M, Stefano GB (1997) Nitric oxide inhibits the dopamine-induced K+ current via guanylate cyclase in Aplysia neurons. *J Neurosci Res* 50: 450–456.
287. Sung YJ, Walters ET, Ambron RT (2004) A neuronal isoform of protein kinase G couples mitogen-activated protein kinase nuclear import to axotomy-induced long-term hyperexcitability in Aplysia sensory neurons. *J Neurosci* 24: 7583–7595.
288. Susswein AJ, Chiel HJ (2012) Nitric oxide as a regulator of behavior: New ideas from Aplysia feeding. *Prog Neurobiol* 97: 304–317.
289. Ye X, Kim WS, Rubakhin SS, et al. (2007) Ubiquitous presence of argininosuccinate at millimolar levels in the central nervous system of Aplysia californica. *J Neurochem* 101: 632–640.
290. Benton JL, Sandeman DC, Beltz BS (2007) Nitric oxide in the crustacean brain: Regulation of neurogenesis and morphogenesis in the developing olfactory pathway. *Dev Dyn* 236: 3047–3060.
291. Scholz NL, Chang ES, Graubard K, et al. (1998) The NO/cGMP pathway and the development of neural networks in postembryonic lobsters. *J Neurobiol* 34: 208–226.
292. Dickinson PS, Calkins A, Stevens JS (2015) Related neuropeptides use different balances of unitary mechanisms to modulate the cardiac neuromuscular system in the American lobster, Homarus americanus. *J Neurophysiol* 113: 856–870.
293. Goy MF (2005) Nitric oxide: An inhibitory retrograde modulator in the crustacean heart. *Comp Biochem Physiol A Mol Integr Physiol* 142: 151–163.
294. Mahadevan A, Lappe J, Rhyne RT, et al. (2004) Nitric oxide inhibits the rate and strength of cardiac contractions in the lobster Homarus americanus by acting on the cardiac ganglion. *J Neurosci* 24: 2813–2824.
295. McGrath LL, Vollmer SV, Kaluziak ST, et al. (2016) De novo transcriptome assembly for the lobster Homarus americanus and characterization of differential gene expression across nervous system tissues. *BMC Genomics* 17: 63.
296. Dyuizen IV, Kotsyuba EP, Lamash NE (2012) Changes in the nitric oxide system in the shore crab Hemigrapsus sanguineus (Crustacea, Decapoda) CNS induced by a nociceptive stimulus. *J Exp Biol* 215: 2668–2676.

297. Filgueira Dde M, Guterres LP, Votto AP, et al. (2010) Nitric oxide-dependent pigment migration induced by ultraviolet radiation in retinal pigment cells of the crab Neohelice granulata. *Photochem Photobiol* 86: 1278–1284.

298. Scholz NL, de Vente J, Truman JW, et al. (2001) Neural network partitioning by NO and cGMP. *J Neurosci* 21: 1610–1618.

299. Scholz NL, Goy MF, Truman JW, et al. (1996) Nitric oxide and peptide neurohormones activate cGMP synthesis in the crab stomatogastric nervous system. *J Neurosci* 16: 1614–1622.

300. Scholz NL, Labenia JS, de Vente J, et al. (2002) Expression of nitric oxide synthase and nitric oxide-sensitive guanylate cyclase in the crustacean cardiac ganglion. *J Comp Neurol* 454: 158–167.

301. Stein W, Eberle CC, Hedrich UB (2005) Motor pattern selection by nitric oxide in the stomatogastric nervous system of the crab. *Eur J Neurosci* 21: 2767–2781.

302. Aonuma H, Nagayama T, Takahata M (2000) Modulatory effects of nitric oxide on synaptic depression in the crayfish neuromuscular system. *J Exp Biol* 203: 3595–3602.

303. Aonuma H, Newland PL (2001) Opposing actions of nitric oxide on synaptic inputs of identified interneurons in the central nervous system of the crayfish. *J Exp Biol* 204: 1319–1332.

304. Aonuma H, Newland PL (2002) Synaptic inputs onto spiking local interneurons in crayfish are depressed by nitric oxide. *J Neurobiol* 52: 144–155.

305. Araki M, Schuppe H, Fujimoto S, et al. (2004) Nitric oxide modulates local reflexes of the tailfan of the crayfish. *J Neurobiol* 60: 176–186.

306. Christie AE, Edwards JM, Cherny E, et al. (2003) Immunocytochemical evidence for nitric oxide- and carbon monoxide-producing neurons in the stomatogastric nervous system of the crayfish Cherax quadricarinatus. *J Comp Neurol* 467: 293–306.

307. Johansson KU, Mellon Jr D (1998) Nitric oxide as a putative messenger molecule in the crayfish olfactory midbrain. *Brain Res* 807: 237–242.

308. Kovaleva VD, Uzdensky AB (2016) Photodynamic therapy-induced nitric oxide production in neuronal and glial cells. *J Biomed Opt* 21: 105005.

309. Mita A, Yoshida M, Nagayama T (2014) Nitric oxide modulates a swimmeret beating rhythm in the crayfish. *J Exp Biol* 217: 4423–4431.

310. Ott SR, Aonuma H, Newland PL, et al. (2007) Nitric oxide synthase in crayfish walking leg ganglia: Segmental differences in chemo-tactile centers argue against a generic role in sensory integration. *J Comp Neurol* 501: 381–399.

311. Schuppe H, Araki M, Aonuma H, et al. (2004) Effects of nitric oxide on proprioceptive signaling. *Zoolog Sci* 21: 1–5.

312. Schuppe H, Newland PL (2004) Nitric oxide modulates presynaptic afferent depolarization of mechanosensory neurons. *J Neurobiol* 59: 331–342.

313. Uzdensky A, Berezhnaya E, Khaitin A, et al. (2015) Protection of the Crayfish Mechanoreceptor Neuron and Glial Cells from Photooxidative Injury by Modulators of Diverse Signal Transduction Pathways. *Mol Neurobiol* 52: 811–825.
314. Christie AE, Fontanilla TM, Roncalli V, et al. (2014) Diffusible gas transmitter signaling in the copepod crustacean Calanus finmarchicus: Identification of the biosynthetic enzymes of nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H₂S) using a de novo assembled transcriptome. *Gen Comp Endocrinol* 202: 76–86.