Sight and insight – on the physiological role of nitric oxide in the visual system

Javier Cudeiro and Casto Rivadulla

Research in the fields of cellular communication and signal transduction in the brain has moved very rapidly in recent years. Nitric oxide (NO) is one of the latest discoveries in the arena of messenger molecules. Current evidence indicates that, in visual system, NO is produced in both postsynaptic and presynaptic structures and acts as a neurotransmitter, albeit of a rather messenger molecules. Current evidence indicates that, in visual system, NO is produced in both postsynaptic and presynaptic structures and acts as a neurotransmitter, albeit of a rather

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VISUAL PROCESSING starts in the retina. Here, the image of the world is broken down through visual filters (the receptive fields of individual neurones). In mammals this visual message then moves to an intermediate station in the thalamus, the dorsal lateral geniculate nucleus (dLGN). This is a laminar structure that receives the ganglion-cell axons in an organized manner depending on the eye from which the image originated, the cell type and other species-dependent characteristics. Finally, this information is relayed to the primary visual cortex (V1) from which connections are made with many other visual cortical and sub-cortical structures. At every level of this pathway, excitatory-amino-acid receptors. However, besides
TABLE 1. Products and targets of neuronal nitric oxide synthase.

<table>
<thead>
<tr>
<th>Nitric oxide-related species</th>
<th>Principal biological target-reactants</th>
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<tbody>
<tr>
<td>N_{2}O</td>
<td>Metals, hydrophilic pockets</td>
</tr>
<tr>
<td>NH_{2}OH</td>
<td>Oxidants</td>
</tr>
<tr>
<td>NO(^{−}) (NO(_{2}); SNO)</td>
<td>Thiols, metals, oxygen</td>
</tr>
<tr>
<td>NO(^{−}) (NO(_{2}); SNO)</td>
<td>Thiols, metals, superoxide, oxygen</td>
</tr>
<tr>
<td>OONO(^{−})</td>
<td>Thiols, metals, tyrosine, methionine</td>
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All of the above nitric oxide (NO\(_{2}\))-related species have been identified from purified preparations of neuronal nitric oxide synthase (NOS). The cellular availability of substrates and cofactors appears to influence the oxidation state of the NOS product. Nitrosyl oxide (NO\(_{2}\)) and hydroxylamine (NH\(_{2}\)OH) are end-reduction products, while nitrosyl-nitrate (NO\(_{3}\); NO\(_{2}\)) are end-reduction products. The remaining compounds have different biological actions and potential sources that reflect their chemistry in different redox milieus. Note that different SNO and MNO species might function as NO\(_{2}\), NO\(_{3}\), or NO donors. Adapted, with permission, from Ref. 22.

Nitric oxide: ubiquitous neurotransmitter or 'saint–sinner'?

Since NO was first recognized as a messenger molecule in the brain that mediates the increased cGMP levels that occur on activation of NMDA receptors, major efforts have been made to understand the extent of its actions. Nitric oxide is a gas synthesized from \(\text{L-arginine}}\) by a number of nitric oxide synthase (NOS). At least three forms of the enzyme have been characterized: the constitutive endothelial and neuronal types are both Ca\(^{2+}\) dependent and the third is a Ca\(^{2+}\)-independent inducible isoform, which is expressed only in the presence of cytokines. In this review, only data related to neuronal NOS (nNOS) will be considered. Available data from immunocytochemistry, in situ hybridization and NADPH-diaphorase histochemistry have given a reasonably comprehensive picture of the anatomical localization of NO-generating cells and their processes throughout the CNS (Ref. 2). The brain contains the highest level of NOS of any tissue so far examined and the broad distribution of the enzyme suggests that NO could be involved in many aspects of CNS function.

However, NO might be a ‘double-edged sword’. In some studies it has been considered to be potentially neurotoxic. Indeed, in the presence of factors such as oxidative stress, generation of reactive oxygen intermediates and deficient antioxidant systems, NO can induce neuronal death. The majority of evidence indicates that the participation of NO in neurodegenerative phenomena occurs through a non-enzymatic reaction with the superoxide anion (O\(_{2}\)^{−}) to form peroxynitrite (ONOO\(^{−}\)) (see Table 1), which is a highly reactive molecule and a potent oxidizing agent. Other mechanisms of NO toxicity, by DNA damage or glutathione depletion have also been postulated.

Fig. 1. Presynaptic and postsynaptic locations of nitric oxide synthase (NOS) and the probable routes of action of nitric oxide (NO). (A) Postsynaptic location of NOS, showing possible presynaptic actions (red arrows). Calcium signal from glutamate-mediated activation of NMDA receptors or voltage-dependent Ca\(^{2+}\) channels (VDCCs) binds calmodulin (CaM) and activates NOS, producing NO and cGMP from \(\text{L-arginine}}\) (reviewed in Ref. 1). The free diffusion of NO suggests that this presynaptic activity need not necessarily be restricted to the presynaptic boutons directly involved with this postsynaptic element. (B) Presynaptic location of NOS, showing possible postsynaptic actions. Note the direct actions on the NMDA receptor, which is expanded in the inset box and shows the different modulatory sites. Neurotransmitter (NT) release is triggered by the arrival of an action potential in the presynaptic terminal by the opening of VDCCs. The resulting elevation in the internal Ca\(^{2+}\) concentration, is the signal that causes NO production. This has been shown to occur in the dorsal lateral geniculate nucleus of the cat\(^{1–12}\), where NO is co-localized with 5-HT within the axons arising from the brainstem\(^{4}\). Again, diffusion of NO can induce actions on sites that are remote from the synapse illustrated here. Therefore, the possibility of combined presynaptic and postsynaptic activities from either NOS location cannot be excluded. Abbreviations: Glu, glutamate; SNAP25, 25 kDa synaptosomal-associated protein; ACh, acetylcholine; NMDA, \(\text{N-methyl-D-aspartate}}\) receptor.
However, these pathological effects remain, to some extent, controversial and confusing. Some laboratories using brain-slice or primary-tissue-culture models of glutamate neurotoxicity have reported that NO is also involved in these pathologies, while others, employing similar methods, have shown no obvious role.

Furthermore, there is also much evidence to suggest that NO might be neuroprotective. Differences between the effects of NO have been attributed, at least in part, to different redox-related species of the NO group and their disparate chemical activities. Neurodestruction has been attributed to peroxynitrite alone and not to NO (the reduced form), and the neuroprotective properties of NO have been attributed to NO•− (the oxidized form), as this species downregulates NMDA-receptor activity by reaction with thiol group(s) in the redox modulation of the receptor78 (Fig. 1).

To complete this brief overview, and yet add another level of complexity, it is important to make clear that, although the best recognized effectors for NO are adenylyl cyclase and cGMP, they are not the only ones and many NO-mediated effects are cGMP independent. These pathways have typically been grouped under the broad heading of renox-related NO signals and can be well-regulated post-translational modifications that are part of cellular control mechanisms. In neurons several enzymes, G proteins, transcription factors, transporters and ion channels are targets for NO (Table 2).

Thus, in brief, NO seems to be an almost ubiquitous messenger substance in the CNS that can, under certain conditions (such as its excessive production or the absence of regulatory control mechanisms), be toxic to cells, while possibly also being capable of acting as a neuroprotectant. However, under normal, physiological conditions NO seems to act as a neurotransmitter, albeit of a novel and unusual type. Within the more restricted field of sensory neurobiology there currently exists a lesser but no less significant interest in NO. Although NO has been demonstrated at all levels of the sensory CNS and across many modalities, there is a large amount of evidence for its presence and action in the visual system (see Fig. 2). Data exist that show NO has a role in the visual system from retina to cerebral cortex and it seems appropriate that a review of these studies is made.

The retina

In a general scheme of vertebrate retinal physiology, visual excitation in photoreceptors is mediated by the light-triggered hydrolysis of intracellular cGMP and is transmitted via bipolar cells to the output, ganglion-cell layer of the retina. The visual signal is laterally modulated by two major classes of neurons: horizontal cells located in the outer plexiform layer and amacrine cells located in the inner retina. Such modulation is carried out via chemical synapses using a number of different neurotransmitters, and also by electrical coupling79. There is now much evidence that demonstrates that NO has a role in the physiological regulation of diverse processes within the retina, from the transduction of the signal by the outer retina to the output of the signal. These include:

**Localization of nitric oxide synthase**

Nitric oxide synthase has been reported to have NADPH-diaphorase (NADPH-d) activity78,79 and both histochemical detection of NADPH-d activity and immunoreactivity to antibodies raised against NOS are used extensively as methods for identifying nNOS. These methods have revealed that horizontal, amacrine and ganglion cells of different mammals contain nNOS, and non-mammals contain rNOS. Moreover, human retinal tissues have been found to express mRNAs for constitutive and inducible NOS (Ref. 31). The presence of rNOS activity in photoreceptors has been a matter of controversy. Several studies using immunocytochemical and NADPH-d histochemical staining failed to localize rNOS activity. Nevertheless, other studies, including the most recent, claim that rNOS activity to be present in the inner and outer segments of photoreceptor rods80,81. Furthermore, using NADPH-d histochemistry to study the cone-dominated retina of the tree shrew it has been possible to reveal several patterns of activity in the cellular subcompartments of the spectral classes of cones, which suggests that NO may be differentially involved in the functioning of different classes of photoreceptors82. Interestingly, there is also evidence that NOS is found in Müller cells of both fish and amphibian species, suggesting yet another route by which NO can modulate retinal function83.

**NO affects the metabolism of cGMP in a variety of cells**

1. Available data show that NO is functionally coupled to a soluble guanylate cyclase and might be able to increase cGMP levels in rod photoreceptors thereby increasing the cGMP-gated conductances, which affect both response amplitude and response kinetics84. Nitric oxide has also been shown to modulate Ca2+ channels and transmission of the photoresponse to second-order cells85, and to increase adenosine diphosphate (ADP) ribosylation of a variety of proteins such as transducin, G proteins and other, as yet unidentified, proteins in the outer segment of photoreceptor rods86–88. These alterations of cellular proteins could be a mechanism by which NO modifies the operational mode of enzymes in the visual transduction cascade. Nitric oxide can also modulate Ca2+ and cyclic-nucleotide-gated channels in both rod and cone photoreceptors, which control excursions at cone synapses, thereby altering synaptic efficacy.

2. Work carried out in fish has shown that NO donors, NOS inhibitors and NO-related substances

<table>
<thead>
<tr>
<th>Targets</th>
<th>Effect</th>
<th>Refs</th>
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<tr>
<td>Guanylate cyclase</td>
<td>LTP, modulation of visual processing at the level of primary visual cortex</td>
<td></td>
</tr>
<tr>
<td>NMDA receptor</td>
<td>Neuroprotection, facilitation of NMDA-mediated responses in dLGN</td>
<td></td>
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<tr>
<td>SNAP25</td>
<td>Synaptic plasticity and transmission</td>
<td>98</td>
</tr>
<tr>
<td>Syntaxin 1a</td>
<td>Synaptic vesicle docking-fusion</td>
<td>99</td>
</tr>
<tr>
<td>syntaxin 1b</td>
<td>Synaptic vesicle docking-fusion</td>
<td>99</td>
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<tr>
<td>Neurograin</td>
<td>LTP, neurotransmitter release</td>
<td>100</td>
</tr>
<tr>
<td>H−ATPase</td>
<td>Vascular glutamate uptake</td>
<td>101</td>
</tr>
<tr>
<td>Cyclic nucleotide-gated channel</td>
<td>Olfactory transduction, modulation of retinal ganglion-cell activity</td>
<td>102</td>
</tr>
<tr>
<td>Ca2+ channel (rod)</td>
<td>Retinal photoreceptor function</td>
<td></td>
</tr>
<tr>
<td>Ca2+ ATPase</td>
<td>LTP, modulation of visual transduction</td>
<td>104</td>
</tr>
</tbody>
</table>

All nitric oxide (NO) targets identified in the CNS to date, with the exception of rNOS, have reactive thiol, that is, those contain cysteines that are potentially subject to general acid-base base modulation. The NMDA receptor and cyclic nucleotide-gated channels are exemplary targets containing the sR (salt-like) motif. Abbreviations: SNAP25, 25 kDa synaptosomal-associated protein; VAMP, vesicle-associated membrane protein. Adapted, with permission, from Ref. 22.
NO has been shown to modulate electrical coupling in horizontal cells in such a way that the presence of cGMP, L-arginine or the NO donor, sodium nitroprusside, decreases electrical and dye-tracer coupling between the cells43–49. This modulation of the gap-junctional conductance seems to be produced in photoreceptors (P), horizontal cells (H), amacrine cells (A), Müller cells (M) and ganglion cells (G) (red)23–36. In the retina it regulates phototransduction42,43; modulates photoreceptor output42,43,47; bipolar cells40 and horizontal cells43–49; controls ganglion-cell excitability40 and modulates the electroretinogram48–51. The widespread distribution of NOS-positive cells in these areas gives rise to possible modulation of retinal processes at all three levels by NO. The time course of effects at each level is likely to be similar because the half-life of NO in vitro has been estimated to be around 6 s (Ref. 52) (although in vivo it could be much longer40). These effects on retinal processing include: (1) regulation of phototransduction (altering levels of cGMP and by ADP ribosylation); (2) modulation of output at photoreceptor synapses (by altering Ca2+ currents); (3) activation of ON-bipolar cells (by acting on its NO-sensitive GC); (4) decreasing the lateral spread of light responses (by decreasing electrical coupling and responsiveness to glutamate in horizontal cells); and (5) controlling ganglion-cell excitability and thereby the retinal output (by acting on cGMP-gated cation channels).

In the cat, monkey and human dorsal lateral geniculate nucleus (dLGN) there are no NOS-positive cells42,43, but they are found in small mammals such as rats and tree shrews58–60. NO donors38. More recently, a cGMP-gated ion channel has been reported after the application of NO donors38. In the cat, monkey and human dorsal lateral geniculate nucleus (dLGN) there are no NOS-positive cells42,43, but they are found in small mammals such as rats and tree shrews58–60. NO donors38. More recently, a cGMP-gated ion channel has been reported after the application of NO donors38.

In mammals, the dLGN plays a pivotal role in the transmission of visual information to the cerebral cortex. Unlike the retina, this is a site where both processing and gating of information takes place – thalamic transmission can be modulated by a number of inputs that arise from the brainstem46 and are dependent upon the behavioural state of the organism. Moreover, processing and gating in the dLGN are also functions that are intimately associated with, and regulated by, neural functioning in the visual cortex, by virtue of the large descending corticofugal input.
Neuronal NOS activity has been found in the thalamus of a variety of species. For example, NADPH-d-positive cells have been seen in the ventral division of the LGN in rats and tree shrews\(^\text{69,70}\), and NADPH-d reactive and GABA (Ref. 60) are co-localized in a sub-population of local inhibitory interneurones in the LGN of the rat\(^\text{71}\). Furthermore, NOS activity has also been detected in the visual thalamus by immunocytochemistry\(^\text{72,73}\). Interestingly, in higher mammals, such as the cat, the monkey and human beings, the LGN are completely devoid of nNOS-containing neurones, although a dense network of axons and terminals are labelled (Fig. 2B; Refs 54–57). Recent evidence has shown that the cat dLGN contains a unique distribution of nNOS, found exclusively within the choliner-gic fibres that originate in the parabrachium\(^\text{74}\). This represents a novel co-localization of neurotransmitters and shows an exclusively presynaptic location for nNOS. It has been demonstrated in vivo that NO can potentially enhance those visual responses that are due specifically and selectively to NMDA-receptor-mediated excitation or mimic the effect of NO donors\(^\text{19}\). Furthermore, NO might affect NMDA-mediated excitation or mimic the action of NO donors\(^\text{19}\).

In summary, in the visual thalamus it can be hypothesized that NO can act wherever brainstem parabrachial terminals arbitrate, with production regulated by activity levels in these fibres in a Ca\(^{2+}\)-dependent manner. While the basal release of NO can contribute to control of oscillatory activity, which is dependent on the behavioural status of an organism, and also facilitate visual transmission from the retina through the LGN to the cortex, particularly when such transmission involves the activation of voltage-dependent NMDA receptors. Furthermore, NO might affect simultaneously the functional status of a relatively large neuronal population by local diffusion. Indeed, a theoretical model has predicted that the sphere of influence of a single point source of NO has a diameter of about 200 μm, corresponding to a volume in the brain that encloses up to two million synapses\(^\text{75}\). A role for NO in the development of subcortical structures

Fig. 3. Summary of the actions of the nitric oxide system in the feline dorsal lateral geniculate nucleus (dLGN). (A) Control visual responses to small spot of light centred over the receptive field centre (centre). Application of the nitric oxide (NO) donor, S-nitroso-N-acetyl-(D,L)-penicillamine (SNAP), increases responsiveness (right). Application of L-NOArg, a nitric oxide synthase (NOS) inhibitor, suppresses visual responses (left). Adapted, with permission, from Ref. 20. (B) Histogram showing that application of the NOS antagonist, L-NOArg, depresses responses to applied NMDA in a highly selective fashion, compared to similar tests with the other drugs KAIN (kainic acid), QUIS (quisqualic acid), AMPA and ACh. Reproduced, with permission, from Ref. 19. (C) Intracellular recordings of a feline geniculate cell in vitro. Example of a neurone that spontaneously generates rhythmic Ca\(^{2+}\)-mediated burst activity. Generation of NO through SIN 1 reversibly inhibits this activity. Indicated segments are expanded for details. Adapted, with permission, from Ref. 63.
vasoactive intestinal polypeptide, the tachykinins or corticotropin releasing factor90. These GABAergic cells also show little or no co-localization with the peptides cholecystokinin, monkey stained according to the protocol of Hope and Vincent89. Moderately and darkly NADPH diaphorase-positive neurones and fibres in the visual cortex (area V1) of a macaque NADPH-diaphorase staining in macaque primary visual cortex. Fig. 4.

REVIEW

tally oriented fibres (f) located in the upper half of layer I. ing numerous lightly or moderately stained neurones (red arrows) and the plexus of horizon-

m in (A) and 35

m in (B) and 35

m in (C). The photomicrographs were provided by Dr Javier DeFelipe, Cajal Institute, Spain. Cortical neurones synthesizing nitric oxide are cur-

rantly visualized with NADPH-diaphorase histochemistry or immunocytochemistry for neuronal nitric-oxide synthase (nNOS). These neurones mainly represent a subpopulation of GABAergic non-pyramidal cells (interneurones) that contain the peptides somatostatin and neuropeptide Y, and frequently contain the Gs- binding protein calbindin, but not parvalbumin and calretinin. These GABAergic cells also show little or no co-localization with the peptides cholecystokinin, vasoactive intestinal polypeptide, the tachykinins or corticotropin releasing factor89.

for remodelling of retinal connections, which coincides with the loss of several transient projections, occurs. This loss is reduced if NO synthesis is inhibited86. Although the exact mechanism by which NO mediates this effect is not clearly understood, it has been suggested that co-

ordinated activity in the major inputs, NMDA-receptor activation and NO production could each have a key role86. Interestingly, in the tadpole explanted retina, application of NO donors results in the collapse of active growth cones of ganglion-cell axons; such a mechanism could explain the termination of axonal growth at the tectal level during development87. Similar results have been found in the dLGN of the ferret and the cat where NOS is transiently expressed during the period in which projections from the retina are refined88,89. In the ferret dLGN, retinal information is segregated into ON-OFF sublaminae, a process that requires NMDA-receptor activation, and application of a NOS inhibitor resulted in an overall pattern of sublamination that was clearly reduced when compared with normal animals90. In the developing kitten in con-

trast with the adult cat, NADPH-d staining of dLGN cells suggested that NO might act in a retrograde fashion and perhaps have a role in the maintenance of associ-

ative processes that underlie activity-dependent refine-

ment of retinogeniculate connections89. Further indirect results on the putative role of NO on development and plasticity have also been obtained in cats. After mon-

ocular lid suturing as kittens, adult cats showed an abnormal presence of NADPH-d-positive cells within the dLGN, which was not seen in normally reared controls, clearly indicating that NO activity can be induced (or perhaps retained) by visual deprivation91.

Visual cortex

In the cerebral cortex, NO production could arise from several possible sources (see Fig. 2C): extrinsi-

cally from cholinergic fibres that originate in the fore-

brain92; from cortical blood vessels capable of NO pro-

duction from endothelial cells of blood-vessel walls93 and intrinsically from cells within the cortex that con-

tain nNOS (a subset of the non-spiny cortical cells94,95). Neurones containing nNOS were observed scattered throughout all cortical regions (Fig. 4) from layers II to VI and in the subcortical white matter in several spe-

cies including the rat94,95, cat92, monkey92,93 and human beings96,97. Such a diversity of production sites suggests a complex role or roles for NO in cortical visual pro-

cessing. Examples to support this include: (1) in primate, the distribution of NOS+/NADPH-d staining is closely aligned with that of cytochrome oxidase and shows a similar laminar and spatial distribution98. This could suggest a role for NOS that is associated with parvocellular, wave-

length selective neurones. (2) Recent evidence has shown that NO might be involved in the NMDA-mediated release of noradrenaline and glutamate from rat cortical synaptosomes, thereby suggesting that NO has both direct actions in the visual cortex and actions on modu-

latory processes99. Investigations centred specifically on the visual cortex of the anaesthetized cat have shown that application of compounds that manipulate the NO system alter responsiveness of a substantial proportion of neurones to visual stimuli, either reducing or aug-

menting visual responses. This regulation of cortical visual processing seems to be mediated via the cGMP second-messenger system70 (Fig. 5) and suggests the existence of both upregulation and downregulation of cellular firing in separate subpopulations of cortical cells, which could be related to the level of cholinergic neurone activity in these cells and with changes in the state of arousal of the animal.

Interestingly, in contrast to studies mentioned above that show a role for NO in the development of subcortical visual structures, there is no evidence to date to suggest a similar developmental role for NO in the visual cortex100, even though NOS distribution in visual cortex can be altered by manipulation of visual inputs101.
Concluding remarks

One of the most intriguing features of NO, considering the simplicity of the molecule, is that it is involved in so many different regulatory functions and has many other effects. At low concentrations, it can work as a neuromodulator or a retrograde messenger in the CNS, at relatively high concentrations it can be toxic. It is tempting to speculate that NO could have multiple roles in separate regions and circuits, each role related to local physiological functions and not necessarily parallel. The more general role that NO has in neurotoxicity or neuroprotection. These represent alterations of normal homeostatic function of the CNS and its regulatory mechanisms. It is important to note the significance of in vivo studies and to understand the need for studies of the physiology of whole systems.

Nitric oxide, the gas, the common air pollutant, the suspected carcinogen and the destroyer of ozone could be the archetypal example used to illustrate the concept of "parasympathetic" information transmission in the brain, a domain of versatility and plasticity, as formulated by Schmidt: "...new ways of conceptualization of information–transactional chemical processes applied as basic concepts of neurobiology", in this case to the concept of vision.

Selected references

The TINS Lecture
Understanding the roles of Otx1 and Otx2 in the control of brain morphogenesis

Dario Acampora and Antonio Simeone

At the 1998 Forum for European Neuroscience, held in Berlin, the plenary lecture by Antonio Simeone was sponsored by TINS. The following article is adapted from that lecture.

The murine homologs of the orthodenticle (otd) gene of Drosophila, Otx1 and Otx2, have an important role in brain morphogenesis. Analysis of Otx1 and Otx2 null mice reveals that Otx1 is required primarily for corticogenesis and sense-organ development, while Otx2 is necessary for specification and maintenance of anterior neural plate as well as for proper gastrulation. Cross-phylum recoveries of Otx1 abnormalities by Drosophila otd, and vice versa, indicate that genetic functions required in mammalian-brain development evolved in a primitive ancestor of flies and mice. Knock-in mouse models in which Otx2 was replaced with Otx1, and vice versa, provide evidence that the existence of Otx1–otd and Otx2–otd divergent phenotypes largely reflects differences in expression patterns rather than in the biochemical activity of Otx1 and Otx2. In evolutionary terms, some of these findings lead us to hypothesize a fascinating and crucial role for Otx genes that contributes to the genetic program required for the specification of the development of the vertebrate head.


IN VERTEBRATES, a remarkable amount of data has been collected in recent years about the role of gene candidates for the control of developmental programs that underlie brain morphogenesis. Most of these genes resemble one another in their ability to regulate a common set of molecular targets, and in their ability to activate similar sets of genes. Among these, the orthodenticle group includes orthodenticle (otd) of Drosophila and the vertebrate Otx1 and Otx2 genes, which contain a bicoid-like homeodomain. In Drosophila, otd, the homeobox-containing gene, empty spiracles (ems) and the zinc-finger gene, button-head (bud) show a partially overlapping expression pattern that includes adjacent head segments. Mutations in each of these three genes cause heavy defects in the anterior head segments where they are transcribed, which suggests that these genes might act as gap genes along the cephalic segments'5. In mouse embryos, the expression patterns of two cognates for Otx1 and Otx2 and two for ems (Juns and Emx1)2 have shown a remarkable similarity with the counterpart genes in Drosophila. This suggests that they might be part of a general control system


87 Bickford, M.E. et al. (1994) J. Comp. Neurol. 348, 481–510


91 Reid, S.N.M. et al. (1996) J. Physiol. 494, 511–517


