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Review

Expression of neuropeptides and their receptors in the developing retina of mammals

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Summmary. The present review examines various aspects of the developmental expression of neuropeptides and of their receptors in mammalian retinas, emphasizing their possible roles in retinal maturation. Different peptidergic systems have been investigated with some detail during retinal development, including substance P (SP), somatostatin (SRIF), vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), neuropeptide Y (NPY), opioid peptides and corticotrophin-releasing factor (CRF). Overall, the developmental expression of most peptides is characterized by early appearance, transient features and achievement of the mature pattern at the time of eye opening. Concerning possible developmental actions of neuropeptides, recent studies imply a role of SP in the modulation of cholinergic neurotransmission in early postnatal rabbit retinas, when cholinergic cells participate in the retinal spontaneous waves of activity. In addition, the presence of transient SRIF expressing ganglion cells and recent observations in SRIF receptor knock-out mice indicate variegated roles of this peptide in the development of the retina and of retinofugal projections. Furthermore, VIP and PACAP exert protective and growth-promoting actions that may sustain retinal neurons during their development, and opioid peptides may control cell proliferation in the developing retina. Finally, a peak in the expression of certain peptides, including VIP, NPY and CRF, is present around the time of eye opening, when the retina begins the analysis of structured visual information, suggesting important roles of these peptides during this delicate phase of retinal development. In summary, although the physiological actions of peptides during retinal development are far from being clarified, the data reviewed herein indicate promising perspectives in this field of study.

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Introduction

The identification of peptide signaling molecules began in the first half of the last century with substance P (SP; Hökfelt et al., 2001) and it has proceeded during the last 30 years with the discovery of numerous peptides, the characterization of their receptors and the exploitation of their physiological actions in the body. Peptidergic messengers were originally isolated (mainly) from the gut or from the hypothalamus and they were interpreted as gastrointestinal or hypothalamic hormones. However, it soon appeared that peptides are distributed to different organs or systems, including the nervous system where they have been designated "neuropeptides" (Hökfelt et al., 2000). Peptides are present in all parts of the nervous system, although each peptide has its unique pattern of distribution. Initially, it was assumed that these "peptidergic" systems were different from and complementary to previously transmitter-characterized neurons, for example those of the catecholamine and serotonin systems. Therefore, an important perspective on neuropeptides, and on chemical transmission in general, was added with the recognition that peptides almost always coexist with one or more classic transmitters (Lundberg, 1996). Functionally, neuropeptides act as neuromodulatory substances, presumably released extrasynaptically. Generally speaking, neuropeptides act on specific receptors to modulate the functional properties of neurons, such as their membrane excitability or their signal transduction pathways. Modern techniques of neuropeptide localization, molecular biology approaches, and the use of transgenic animals have prompted an enormous growth in the knowledge of neuropeptide expression and neuropeptide receptor pharmacology and diversity. However, in spite of the wide variety of information gathered on peptidergic systems and the availability of ultra-sensitive techniques, it has been difficult to define

an exact physiological role for many of the neuropeptides in the nervous system. There are, of course, examples of neuropeptide participation in specific functions or hints of neuropeptide involvement in certain behavioral states or mental diseases. For instance, SP and opioid peptides are involved in the transmission and modulation of pain (Harrison and Geppetti, 2001; Przewlocki and Przewlocka, 2001); SP and its receptor (the neurokinin 1 receptor, NK1) are implicated in depression (Harrison and Geppetti, 2001; Rupniak, 2002) and in memory-promoting, reinforcing and anxiolytic-like effects (Hasenohrl et al., 2000); SP, colecystokinin and opioid peptides participate in the regulation of aggressive behavior (Siegel et al., 1999); opioid peptides may regulate striatal output pathways and motor behavior (Steiner and Gerfen, 1998); pituitary adenylate cyclase-activating polypeptide (PACAP) is involved in the regulation of hypothalamic neurosecretion, homeostatic control of circadian clock and learning and memory processes (Zhou et al., 2002); vasoactive intestinal polypeptide (VIP) modulates the strength of glutamate-mediated neurotransmission in the cortex (Magistretti et al., 1998); somatostatin (somatotropin release-inhibiting factor, SRIF) affects electrophysiological properties of neurons and modulates classical neurotransmission with effects on cognitive, locomotor, sensory, and autonomic functions (Patel, 1999); corticotropin releasing factor (CRF) is implicated in stress-related disorders such as anxiety and depression (Reul and Holsboer, 2002), in learning and memory (Croiset et al., 2000), in pain and analgesia (Lariviere and Melzack, 2000) and in the modulation of ingestive behavior (Heinrichs and Richard, 1999); and neuropeptide Y (NPY) may have a role in neuronal excitability, learning and memory, anxiety-related behaviors, feeding, regulation of blood pressure and circadian rhythm (Thorsell and Heilig, 2002). Given the wide spectrum of (possible) neuropeptide actions, a novel approach in the study of neuropeptides has been undertaken in recent years based on the production of peptide analogs with agonistic or antagonistic properties. These lines of research have produced a variety of peptide and nonpeptide agonists and antagonists that are specific for distinct peptide receptor subtypes, including SP (Hökfelt et al., 2001), SRIF (Hannon et al., 2002), VIP (see for instance Levy et al., 2002; Reed et al., 2002), CRF (Takahashi, 2001) and TRH (Kubek and Garg, 2002) receptors. These compounds constitute important new tools to investigate the functional roles of neuropeptides and the pharmacology of their receptors. In addition, the study of peptide analogs may lead to the development of compounds with therapeutic potential in a variety of disease states. For instance, SP antagonists at the NK1 receptor have been revealed as effective antidepressant and anxiolytic agents (Hökfelt et al., 2001; Rupniak, 2002).

Besides their multifaceted actions in the mature animal, neuropeptides may play functional roles of fundamental importance during the maturation of the nervous system. This idea may arise considering that, in the developing nervous system, neuropeptides, along with their receptors, are usually expressed at early times, when synaptic connections are still immature. In addition, transient expression of neuropeptides or developmentally regulated peptide expression have been reported in distinct brain regions, suggesting peptides may mediate functional interactions associated with the morphological and functional development of the nervous system. During this period, neuropeptides may affect a variety of parameters, including cell division, neuronal survival, neurite sprouting, growth cone motility, and neuronal and glial phenotype (Emerit et al., 1992; Müller et al., 1995; DiCicco-Bloom et al., 1998, 2000; Gressens, 1998; Hauser and Mangoura, 1998; Lindholm et al., 1998; Raffa, 1998; Schwartz et al., 1998; Yew et al., 1999; Gozes and Brenneman, 2000; Kwong et al., 2000; Hansel et al., 2001a,b; Waschek, 2002). Some of these actions are direct while others are mediated by the production of neurotrophic factors from glial cells (Gozes and Brenneman, 2000). Neuroprotective and/or neural growth-related actions have been well documented for tachykinin peptides, VIP, PACAP, SRIF, NPY and opioid peptides (Emerit et al., 1992; DiCicco-Bloom et al., 1998; Gressens, 1998; Hauser and Mangoura, 1998; Raffa, 1998; Schwartz et al., 1998; Gozes and Brenneman, 2000; Hansel et al., 2001a, b; Waschek, 2002; Zagon et al., 2002; Zhou et al., 2002).

The present paper will focus on the relevant aspects of neuropeptide expression during development in a specific region of the central nervous system, the retina. A comprehensive examination of the peptidergic systems of the brain or a detailed description of the peptidergic cell populations of the mature retina are far beyond our scopes, and these aspects have been extensively treated in many recent and past review works. However, before presenting the available data on neuropeptide expression in developing retinas, we think it is necessary to briefly recapitulate the main peptidergic systems in view of their possible roles in neural development and to summarize the organizational plan of the mammalian retina as well as its development.

Peptidergic systems and neural development

In this section, main peptidergic systems which have been found to be involved in developmental processes of the nervous system will be summarized. Data of the retina are not reported, as they will be reviewed in more detail in the following paragraphs.

Tachykinin peptides

The family of tachykinin peptides includes SP, neurokinin A, neurokinin A-related peptides (neuropeptide K and neuropeptide γ) and neurokinin B. Two distinct, structurally related genes encode for these peptides: SP, neurokinin A and neurokinin A-related

peptides are the protein products of the preprotachykinin A gene, while neurokinin B is encoded by the preprotachykinin B gene (Otsuka and Yoshioka, 1993). The cellular actions of the tachykinin peptides are mediated by specific, high affinity receptors. The tachykinin peptides SP, neurokinin A and neurokinin B are the preferred ligands for the neurokinin receptors, belonging to the superfamily of G protein-coupled receptors and termed NK1, NK2 and NK3, respectively (Otsuka and Yoshioka, 1993).

The preprotachykinin A is expressed early in the embryonic development of the nervous system (MacKenzie and Quinn, 2002), while the expression of NK1 receptor mRNA has been reported to be developmentally regulated in distinct regions of the rat brain (Taoka et al., 1996), suggesting a role of SP in brain development. This hypothesis is supported by observations of neuroprotective and growth-promoting actions of SP in a variety of models of the nervous system. Indeed, SP has been shown to counteract the depletion of cortical noradrenergic terminal projections induced by 6-hydroxydopamine administration in newborn rats (Jonsson and Hallman, 1982) and in kittens (Nakai and Kasamatsu, 1984), suggesting that SP may prevent cortical neuronal damage during development. In addition, SP enhances nerve growth factor-mediated neurite outgrowth (Narumi and Fujita, 1978), while SP binding sites have been shown in a growth cone-enriched fraction of developing rat forebrain (Lockerbie et al., 1988). Furthermore, SP has been reported to promote neurite outgrowth in cultured spinal cord of rat embryos (Iwasaki et al., 1989), and SP released by pioneering pathways may interact with NK1 receptors expressed by cells in the floor plate to promote the release of a chemoattractant to guide the permanent axons (De Felipe et al., 1995). Together, these data suggest that SP may act as a growth factor during the development of the nervous system.

SRIF

SRIF was first identified in the hypothalamus as a tetradecapeptide that inhibited the release of growth hormone (Brazeau et al., 1973). SRIF is best regarded as a phylogenetically ancient multigene family of peptides with two important bioactive products, SRIF-14, the form originally identified in the hypothalamus, and SRIF-28, a congener of SRIF-14 extended at the N-terminus that was discovered subsequently (Pradayrol et al., 1980). SRIF-28 accounts for 20-30% of total immunoreactive SRIF in the brain, but it is not clear whether it is cosynthesized with SRIF-14 or whether it is produced in separate neurons (Patel, 1999). SRIF-14 predominates in pancreatic islets, stomach, and neural tissues and is virtually the only form in retina, peripheral nerves, and enteric neurons (Patel, 1999). SRIF-positive neurons and fibers are widely distributed throughout the central nervous system with the notable exception of the cerebellum (Johansson et al., 1984).

Five different SRIF subtype receptors have been cloned and designated sst_1 through sst_5 receptors (Patel, 1999). Although there is a high degree of sequence and structural homology among different SRIF receptors, they differ in their pharmacological and functional properties. For instance, sst_1 and sst_2 receptors differ in their affinity to specific SRIF agonists and in their modes of transmembrane signaling (Csaba and Dournaud, 2001). Both sst_1 and sst_2 receptors are coupled to inhibition of adenylate cyclase, but sst_2 receptor, and not sst_1 receptor, internalizes or desensitizes after exposure to the agonist. These diversities may underlie different functional roles of the two receptors. In particular, although both sst_1 and sst_2 receptors are involved in regulation of growth hormone secretion (Lanneau et al., 2000), sst_1 receptor may also act as an autoreceptor and inhibit SRIF release (Helboe et al. 1998). In addition, activation of sst_1 receptor increases nerve cell responses to glutamate whereas activation of sst_2 receptor results in a decrease of glutamate sensitivity (Lanneau et al. 1998). Moreover, sst_2 receptor, but not sst_1 receptor, has been reported to regulate Ca^{2+} influx through voltage-gated Ca^{2+} channels (Petrucci et al., 2000).

In prenatal neurons, SRIF and its receptors are expressed early and transiently, but little is known about their function at these early stages (Leroux et al., 1995). The early expression of SRIF and of its receptors may indicate that this peptidergic system participates in the control of neuronal maturation (Bulloch, 1987; Grimm-Jorgensen, 1987; Gonzalez et al., 1992; Taniwaki and Schwartz, 1995; Schwartz et al., 1998; Traina et al., 1998). A variety of studies support a developmental role for SRIF by documenting its early onset, its transient expression and its morphogenetic effects. In particular, SRIF enhances neurite outgrowth (Bulloch, 1987; Grimm-Jorgensen, 1987; Taniwaki and Schwartz, 1995), potentiates the expression of K^+ and Ca^{2+} channels (Rhie et al., 1999) and influences neuronal migration (Yacubova and Komuro, 2002). In addition, alterations of endogenous SRIF levels have been shown to severely affect neuronal maturation (Kungel et al., 1997; Fontanesi et al., 1998).

VIP and PACAP

VIP and PACAP are members of the secretin/glucagon/VIP/PACAP/growth-hormone-releasing hormone family (Zhou et al., 2002). VIP is a 28-amino acid peptide, which was first isolated from the gastrointestinal tract (Said and Mutt, 1970). VIP and the related neuroactive peptide, peptide histidine isoleucine are synthesized from the same precursor mRNA and are derived from a common precursor protein (Itoh et al., 1983). Two PACAP isoforms have been described, one with 27 (PACAP-27) and one with 38 (PACAP-38) amino acids. PACAP-27 is identical to the N-terminal of PACAP-38 (Zhou et al., 2002).

VIP and PACAP receptors belong to the same family

of G protein-coupled receptors. Two types of binding sites for PACAP have been described. In type I sites PACAP binds with high affinity and VIP with a much lower affinity, while type II binding sites have similar affinity for PACAP and VIP. Molecular cloning has revealed three distinct PACAP receptor subtypes: a PACAP-specific PAC1 receptor, and two receptors with similar affinity for PACAP and VIP, denominated VPAC1 and VPAC2 receptors, with VPAC2 receptors also displaying high affinity for helodermin. Eight splice variants of the PAC1 receptor originate from a common gene by alternative splicing. PAC1 receptors are functionally coupled to adenylyl cyclase and to phospholipase C, while VPAC1 and VPAC2 receptors are primarily coupled to adenylyl cyclase (Zhou et al., 2002).

A developmental regulation of VPAC1 has been reported in mouse brain, suggesting a role for VIP in neuronal differentiation (Karacay et al., 2000). In fact, past and recent studies have established growth factor and neuroprotective roles for VIP. It promotes mitosis, growth and survival of immature neuronal elements in culture (Brenneman et al., 1985; Brenneman and Eiden, 1986; Pincus et al., 1990; Iwasaki et al., 2001), it is an important regulator of embryonic growth (Gressens et al., 1993; Spong et al., 1999) and it has resulted effective in protecting neural cells in a variety of situations (Gozes et al., 1996; Gressens et al., 1997; Zupan et al., 2000). These positive actions of VIP are likely to be mediated by factors released by glial cells upon VIP stimulation, including activity-dependent neurotrophic factor and related proteins (Gozes and Brenneman, 2000) and insulin growth factor-I (Servoss et al., 2001).

Trophic and protective action in the nervous system are also exerted by PACAP (Waschek et al., 2000). The expression of both PACAP and PAC1 receptor is developmentally regulated in the rat brain (Lindholm et al., 1998; Jaworski and Proctor, 2000). In addition, PACAP has been reported to regulate neurogenesis in the cerebral cortex (DiCicco-Bloom et al., 1998; Suh et al., 2001), in the cerebellum (Vaudry et al., 1999), in the olfactory epithelium (Hansel et al., 2001a) and in the superior cervical ganglion (DiCicco-Bloom et al., 2000). Interestingly, while PACAP exhibits an anti-mitogenic activity in the cerebral cortex (DiCicco-Bloom et al., 1998; Suh et al., 2001), it stimulates mitoses in the cerebellar cortex (Vaudry et al., 1999). There is also evidence of neuroprotective effects of PACAP against apoptotic cell death induced by different factors in cerebellar neurons (Vaudry et al., 2002a, b). In addition, PACAP increases the survival and promotes neurite outgrowth of cultured dorsal root ganglia neurons, where it also induces expression of calcitonin gene-related peptide (Lioudyno et al., 1998). Finally, both PACAP and VIP have been reported to affect the morphological development of cultured sympathetic neurons (Drahushuk et al., 2002).

Together, these data strongly support the evidence for important regulatory actions of both PACAP and VIP in the development of the nervous system.

NPY

NPY is a member of a peptide family that also includes the hormones peptide YY and pancreatic polypeptide (Larhammar, 1996). These peptides act on a common set of G protein-coupled receptors designated NPY receptors (Michel et al., 1998). Functional studies with agonists and molecular cloning have identified five different NPY receptor subtypes designated Y1, Y2, Y4, Y5 and Y6, while the existence of a Y3 receptor has also been postulated (Michel et al., 1998). These receptors act through the inhibition of adenylate cyclase and signaling responses in neurons include inhibition of Ca^{2+} channels (Michel et al., 1998).

NPY is broadly expressed in the developing nervous system and is maintained at moderately high levels in the adult (Danger et al., 1990). NPY expression is transiently upregulated, during development, in specific compartments of the rat inferior olivary complex, supporting the hypothesis that NPY may exert different trophic-differentiating and/or neuromodulatory roles during development of this structure (Morara et al., 1997). NPY is a potent inductor of neuronal proliferation in the olfactory epithelium (Hansel et al., 2001a,b). In addition, NPY expressed by Schwann cell precursors might have a role in axonal growth or axonal guidance (Ubink and Hökfelt, 2000). The effects of NPY on growing axons may be indirect, as demonstrated in primary cultures of adult rat DRG: in this case, NPY stimulates the release of NT-3 from spinal cord slices in the same culture, which in turn stimulates neurite outgrowth from DRG neurons (White, 1998). Finally, in neurons cultured from the developing suprachiasmatic nucleus, where GABA is an excitatory transmitter, NPY exerts a long-term depression of GABA-mediated Ca^{2+} rises, suggesting that NPY-secreting cells may modulate the effects of GABA on neurite outgrowth, gene expression, and physiological stimulation (Obrietan and van den Pol, 1996).

Opioid peptides

The family of opioid peptides is composed of a multiplicity of endogenous opioid ligands that activate G protein-coupled receptors denominated μ, δ, κ and ε. In particular, endomorphin-1 and endomorphin-2 act on μ-opioid receptors, enkephalins act on δ-opioid receptors, dynorphin-A_{1-17} acts on κ-opioid receptors, and ß-endorphin acts on ε-opioid receptors (Nock et al., 1993; Tseng et al., 1995).

Opioid peptides act as growth factors in neural and non-neural cells and tissues. In particular, [Met^5]-enkephalin plays an important role as a tonic inhibitor regulating cell proliferation and tissue organization during development. It acts on a specific receptor that is different from the other previously identified opioid receptors. The biology of this peptide, denominated

"opioid growth factor" and of its receptor have been recently reviewed (Zagon et al., 2002).

Other peptides

A number of other peptides have been postulated to exert some effects on neural development in different models of the nervous system. For instance, CRF may be involved in regulating the development of mouse cerebellar neurons and glia immediately after birth (Ha et al., 2000; Bishop, 2002), and the CRF antagonist, α-helical CRF, has a neuroprotective effect in ischemic or excitotoxic injury of the brain (Lyons et al., 1991; Strijbos et al., 1994). In addition, angiotensin peptides inhibit neurite outgrowth in embryonic chick sympathetic neurons in culture (Reed et al., 1996), while cholecystokinin may exert neuroprotective actions in development, as it protects adult sympathetic neurons from 6-hydroxydopamine-induced lesions in mice (Manni et al., 2001). Finally, galanin has been postulated to be involved in processes taking place during brain maturation (Burazin et al., 2000).

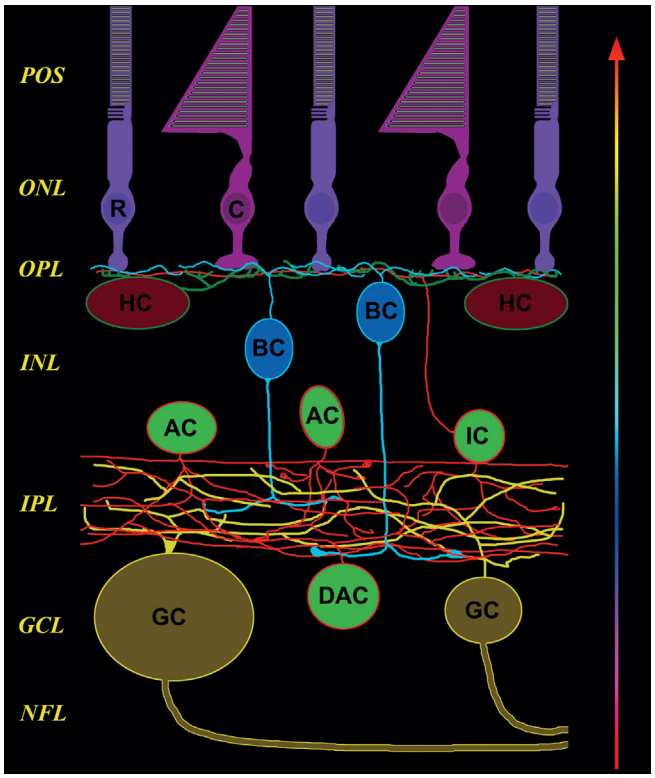


Fig. 1. Structure of the mammalian retina. Retinal layers: POS, photoreceptor outer segments; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; NFL, nerve fiber layer. Retinal cells: AC, amacrine cell; BC, bipolar cell; C, cone; DAC, displaced amacrine cell; GC, ganglion cell; HC, horizontal cell; IC, interplexiform cell; R, rod. Arrow indicates the direction of incoming light.

The retina and its development

The vertebrate retina has been extensively used as an experimental model of the central nervous system for many years. The retina displays the complexity typical of the brain while having an ordered, layered structure that is conserved throughout its extension (Fig. 1). It is part of the central nervous system and it is separated at the same time, allowing easy experimental approaches. Its location within the eye makes the in vivo situation quite similar to an in vitro setup, in which the eye chamber may be regarded as a "natural incubator" of the retinal tissue and the vitreous humor as a culture medium that can be easily manipulated by, for instance, intraocular injections of pharmacological agents.

The structure and organization of the vertebrate retina has been extensively reviewed (for recent reviews see Bloomfield and Dacheux, 2001; Kolb et al., 2001; Masland, 2001a,b). The retina is composed of five classic neuronal cell types, including photoreceptors, bipolar, horizontal, amacrine, and ganglion cells. A sixth type is that of interplexiform cells, that may be considered an amacrine cell variant (Wässle and Boycott, 1991). The basic circuitry within the retina directs the flow of visual information from photoreceptor cells, through bipolar cells, to ganglion cells. Two horizontal pathways modulate this flow: one provided by horizontal cells in the outer retina, the other formed by amacrine cells in the inner retina (Fig. 2). Ganglion cells are the only output neurons in the retina and their axons constitute the retinofugal projections to the brain. A wide variety of neuroactive substances are expressed in the retina. The most heterogeneous retinal cell type is that of amacrine cells. They can be divided into numerous sub-populations on the basis of their neurochemical phenotypes.

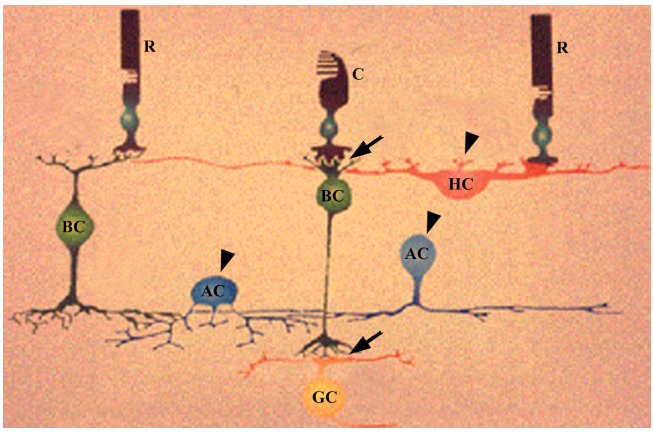


Fig. 2. Visual information flows through synapses between photoreceptors, bipolar cells and ganglion cells (arrows). This vertical pathway is modulated at two distinct levels by horizontal and amacrine cells (arrowheads). Abbreviations as in figure 1.

Retinal layers and neuronal subtypes

The layered structure of the retina and the retinal neuronal cell types are depicted in figure 1. The outermost retinal layer is that of the photoreceptor outer segments, followed (proceeding toward the vitreous chamber) by the outer nuclear layer which is formed by the photoreceptor (rods and cones) somata. The outer plexiform layer (OPL) contains the synaptic contacts between photoreceptors, bipolar cell dendrites and horizontal cells. Bipolar cells can be functionally divided into two main types, ON and OFF, according to their response to light. Morphologically, ON and OFF types are distinguished by the location of their terminal arborizations in the inner plexiform layer (IPL; see below): ON-type bipolar cells arborize in sublamina *b* (proximal half), while OFF-type bipolar cells arborize in sublamina *a* (distal half) of the IPL (Euler and Wässle, 1995; Hartveit, 1997). Bipolar cells can also be distinguished in rod bipolar cells and cone bipolar cells, according to the type of photoreceptor they contact. There is only one type of rod bipolar cell and it displays ON responses (Wässle et al., 1991), while according to a recent review (Masland, 2001b) mammalian retinas may contain between 9 and 11 different types of cone bipolar cells which represent either ON or OFF functional types. In most mammals, there are two morphologically distinct types of horizontal cells (Masland, 2001b). Proximal to the OPL, the inner nuclear layer (INL) contains the cell bodies of horizontal, bipolar, amacrine and interplexiform cells. Typically, horizontal and bipolar somata are located in the half of the INL near the OPL, while amacrine cells are located near the IPL. The main morphological characteristic to differentiate amacrine cells into two broad categories is the extension of their dendritic fields, and they can be grouped into narrow- or wide-field amacrine cells (Brecha et al., 1991). In fact, amacrine cells represent the most variegated cell type in the retina, with 29 different identified subtypes (Masland, 2001b) composed of morphologically and neurochemically distinct populations. If glutamate is the neurotransmitter of the vertical retinal pathways (photoreceptor to bipolar cells to ganglion cells), many different neuroactive substances are used by amacrine cells. Broad populations of amacrine cells are those represented by glycinergic and GABAergic amacrine cells. Among GABAergic amacrine cells, a number of subpopulations are defined on the basis of the coexistence of GABA together with another neuroactive substance (Strettoi and Masland, 1996). For instance, the "starburst" amacrine cells contain both acetylcholine and GABA (Brecha et al., 1988), while others are characterized by the presence of a specific peptide (see for instance Hutsler and Chalupa, 1994; Vigh et al., 2000; Cristiani et al., 2002). In the IPL, the synaptic contacts between bipolar cell axons, ganglion cell dendrites and amacrine cell processes are contained. Within the IPL, five sublayers, called "laminae" (Cajal, 1893), can be identified. In the ganglion cell layer (GCL) 10-15 different types of ganglion cells have been described, and they differ both in morphology and in physiology (Masland, 2001b). Up to 18 different types of ganglion cells have been recognized in the human retina (Kolb et al., 1992). The ganglion cell axons run within the nerve fiber layer (NFL) and they converge toward the optic disk to form the optic nerve.

Retinal development

The development of mammalian retinas proceeds under the harmonic control of genetic and epigenetic factors which co-operate to achieve a suitable morpho-functional organization of retinal circuitry to efficiently analyze the visual environment. In the embryonic period, the proper cell types in the proper ratio are produced. Subsequently, they migrate to the proper layer, differentiate, form synaptic connections and establish their functional properties (Garey, 1984; Nishimura and Rakic, 1987; Kalil, 1990; Messersmith and Redburn, 1993; Rich et al., 1997; Provis et al., 1998; Cook and Chalupa, 2000; Mey and Thanos, 2000; Livesey and Cepko, 2001; Reese and Galli-Resta, 2002). Processes such as the acquisition of characteristic neurochemical phenotypes or the maturation of cell morphology may require an extended postnatal period and they are mostly achieved around the time of eye opening (Ferriero and Sagar, 1987, 1989; Zhang et al., 1990; Zhang and Yeh, 1991; Casini et al., 1994, 1997b, 1998; Rich et al., 1997; Lyser et al., 1999; Greka et al., 2000; Johansson et al., 2000a,b; Bai et al., 2001), although some characteristics are not fully developed until very late developmental periods. For instance, the complete morphological features of dopaminergic amacrine cells and of rod bipolar cells in the rabbit retina are achieved well after eye opening (Casini and Brecha, 1992a; Casini et al., 1996).

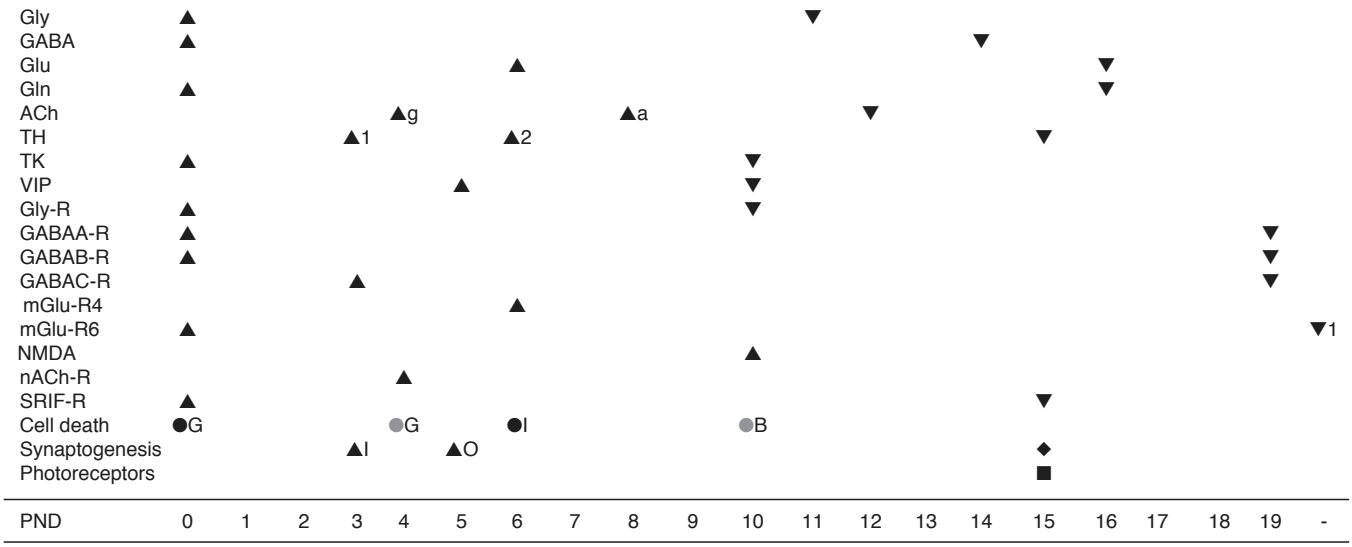
In the rabbit retina, a few synaptic specializations in the IPL are observed prenatally (Greiner and Weidman, 1982), and a low density of synaptic contacts is reported during the first postnatal week (McArdle et al., 1977). Between postnatal day (PND) 9 and PND 11 there is a major increase in the synaptic density, which becomes comparable to that in the adult by PND 20 (McArdle et al., 1977). The rapid phase of the increase in synaptic density in the IPL roughly corresponds to the time of eye opening (around PND 10). Functionally, by PND 10 the majority of ganglion cells can be activated by light, and their receptive field characteristics are mature by PND 20 (Masland, 1977). Similarly, in rat retinas the peak of synaptic formation in the IPL is reported around PND 12 (Horsburg and Sefton, 1987; Sassoè-Pognetto and Wässle, 1997), while eye opening is around PND 15. Before eye opening there is also a consistent remodeling of ganglion cell dendrites in the IPL (Yamasaki and Ramoa, 1993) and ganglion cell death that in the rat encompasses the first ten postnatal days (Potts et al., 1982; Perry et al., 1983). The presence of synaptic

specializations in the IPL during the early postnatal period (Sassoè-Pognetto and Wässle, 1997) and the appearance of synaptic vesicle proteins in the IPL at PND2 (Sarthy and Bacon, 1985; Dhingra et al., 1997) indicate that transmitters may be released and act, either in a synaptic or in a paracrine fashion, at early postnatal ages. A summary of the development of the rat retina (including the appearance of transmitter systems) is reported in Table 1.

During retinal development, horizontal synaptic connectivity develops before the vertical connections that transmit visual information in the adult. At birth, the outer segments of photoreceptors are still immature, and it takes around 10-15 days for the phototransductive cascade to be prepared to respond to light (Blanks et al., 1974; el Azazi and Wachtmeister, 1993). Photoreceptor maturation strongly influences the development of bipolar cells. For instance, the mature pattern of expression of glutamate receptors in bipolar cells is reached together with the functional maturation of photoreceptors (Pow and Barnett, 2000). In addition, major defects have been demonstrated in rod bipolar cells in a retinal model of photoreceptor degeneration, indicating that photoreceptor integrity is important for a correct maturation of bipolar cells (Strettoi et al., 2002). The genesis of amacrine cells encompasses the mid and late prenatal, and early postnatal periods in most mammalian retinas (Stone, 1988; Schnitzer, 1990; Rapaport and Vietri, 1991). As to retinal ganglion cells, the process of their dendritic segregation in the IPL starts before birth, but the ribbon synapses from afferent bipolar cells are not fully developed until late postnatal ages (Horsburgh and Sefton, 1987; Koulen, 1999). Taken together, these data indicate that the retinal microenvironment before eye opening is highly permissive for the active growth of neuronal processes and synapse formation. After eye opening, there may be changes in the chemical composition of the retinal microenvironment that would become less and less permissive for process outgrowth, allowing synapses to be stabilized, morphological features to be completed and transduction of visual stimuli initiated.

Multiple molecular signals are likely to participate in the regulation of retinal development (Sharma and Johnson, 2000). The expression of most neuroactive substances in retinal development is first observed at late prenatal or early postnatal periods, when photoreceptor outer segments are undifferentiated, synaptogenesis in the IPL is very poor and electroretinographic responses are not detected. It appears that most neurotransmitters are expressed before retinal circuitries are capable of visual information processing, and the expression of neuroactive molecules at these early times may be functionally related to developmental events. For instance, in the rabbit retina, dopaminergic amacrine cells are first detected at embryonic day 26, which is four to five days before birth (Mitrofanis et al., 1992), and they acquire most of their mature characteristics by the time of eye opening (Casini and Brecha, 1992a,b). Similarly, cholinergic amacrine cells have been detected at late embryonic/early postnatal ages in rat, cat, ferret, tree shrew and opossum retinas (Mitrofanis et al., 1989a;

Table 1. Summary of the development of the rat retina.



Gly: glycine; Glu, glutamate; Gln: glutamine; ACh: acetylcholine; R: receptor. ▲: first appearance; ▲: g ACh in ganglion cells; ▲ a: ACh in amacrine cells; ▲1 TH in class 1 TH-containing amacrine cells; ▲2 TH in class 2 TH-containing amacrine cells; ●G Cell death in GCL; ●I Cell death in INL; ●G: peak of cell death in ganglion cells; ●B: peak of cell death in bipolar cells; ▲I Synaptogenesis in IPL; ▲O Synaptogenesis in OPL; ◆: peak of synaptogenesis; ◆ m: aturation of photoreceptor outer segments;▼: mature pattern; ▼: mature pattern at PND 28.

Feller et al., 1996; Koulen, 1997; Sandmann et al., 1997; Camargo De Moura Campos and Hokoç, 1999) and GABA as well as NMDA receptors are present in the early postnatal rat retina (Hartveit et al., 1994; Sassoè-Pognetto and Wässle, 1997; Koulen et al., 1996, 1997, 1998a,b).

A characteristic of developing vertebrate retinas is the presence of the spontaneous "waves" of activity in the inner retina. Indeed, spontaneous electric activity leading to synchronized oscillations in intracellular Ca^{2+} concentration has been reported in amacrine and ganglion cells of developing retinas (Wong, 1995, 1998; Wong et al., 1995). Correlated firing of retinal ganglion cells is likely to contribute to the formation of correctly organized ganglion cell projections onto primary visual targets in the brain (Goodman and Shatz, 1993; Katz, 1993; Wong et al., 1993). Different transmitter systems may be responsible for different phases of spontaneous wave activity (Wong et al., 2000; Zhou and Zhao, 2000; Zhou, 2001a), although cholinergic mechanisms seem to play a central role (Zhou, 2001b; Feller, 2002).

Summary of peptidergic systems in mammalian retinas

Several peptidergic systems are expressed in mammalian retinas. In this paragraph, we will briefly summarize the main aspects of peptide expression in mammalian retinas.

Neuropeptides are generally localized in the inner retina and they are expressed by amacrine, displaced amacrine and ganglion cells. Neuropeptide receptors are widely expressed by numerous retinal cell populations, suggesting that peptidergic cells participate in multiple circuits mediating visual information processing. The differences observed between the localization of peptide-containing processes and the distribution of peptide receptors suggest that peptides act in a paracrine manner and have a broad influence on retinal circuits both in the outer and in the inner retina. Functional studies show that exogenous application of peptides modulates transmitter release from the retina (Bruun and Ehinger, 1993; Dal Monte et al., 2003a) and influences the cellular activity of bipolar, amacrine and ganglion cells (Zalutsky and Miller, 1990a,b). The signal transduction via G-protein-coupled receptors determines the activation/inactivation of multiple intracellular effectors, including cAMP and Ca^{2+}, and the modulation of K^+ and Ca^{2+} channels, and of GABAA receptors (Colas et al., 1992; Veruki and Yeh, 1992; Bruun et al., 1994; Feigenspan and Bormann, 1994; Akopian et al., 2000; Johnson et al., 2001; Petrucci et al., 2001). Peptides are often co-expressed with GABA in populations of wide-field amacrine cells. For instance, co-localization of GABA with NPY, SP or VIP has been reported in amacrine cell types of rat, rabbit, cat and monkey retinas (Vaney et al., 1989; Caruso et al., 1990; Casini and Brecha, 1992c; Cuenca and Kolb, 1998; Oh et al., 2002). In addition, PACAP is co-expressed with glutamate in ganglion cells projecting to the suprachiasmatic nucleus of the hypothalamus (Hannibal et al., 2000).

Peptidergic systems identified in mammalian retinas include tachykinin peptides, VIP, PACAP, SRIF, NPY, opioid peptides, CRF, TRH, angiotensin and others (Table 2). Recent data on peptide receptor localization allow a better understanding of peptidergic influences within the retina. For instance, NK1 receptors, whose preferred ligand is SP, are localized to dopaminergic amacrine cells both in rat (Casini et al., 1997a) and in rabbit (Casini et al., 2002) retinas. This finding is consistent with the observation that SP or an SP agonist elicit dopamine release in the rabbit retina, while an SP antagonist significantly reduces basal dopamine levels (Casini et al., submitted), suggesting that dopamine levels in the retina are strictly controlled by the SP-expressing amacrine cell population. Interestingly, the expression pattern of NK1 receptors varies among species. In the rat retina, for example, NK1 is mainly expressed by GABAergic interplexiform and amacrine cells, by adrenergic and most of the dopaminergic amacrine cells (Casini et al., 1997a), whereas in the rabbit retina it is expressed in a distinct population of cone bipolar cells and in all the dopaminergic amacrine cells (Casini et al., 2002). These differences are likely to be related to species-specific behavioral habits.

SRIF receptors have also been carefully investigated in the retina. Immunocytochemical data show that they are expressed by numerous cell populations, suggesting SRIF actions at multiple levels of retinal circuitry. In

Table 2. Localization of main peptidergic systems in mammalian retina.

	MOUSE	RAT	GUINEA PIG	RABBIT	CAT	PIG	PRIMATE
Tachykinins	AC, DAC	AC*, DAC, GC	AC, DAC	AC*, DAC, GC	AC*, DAC		AC*, DAC, GC
SRIF	AC, DAC	AC, DAC	AC, DAC	DAC	DAC, GC		AC, DAC, GC
VIP	AC	AC*	AC	AC*, DAC	AC*	AC	AC*
PACAP		AC, GC, HC					
NPY	AC, DAC	AC*, DAC	AC		AC*, GC	AC	AC*, GC
Opioids			AC				
CRF		AC, DAC					AC, DAC
CCK					AC, HC		AC, BC

AC: amacrine cells; BC: bipolar cells; DAC: displaced amacrine cells; GC: ganglion cells; HC: horizontal cells. *: Colocalization with GABA.

particular, the sst_1 receptor is predominantly expressed by SRIF-containing amacrine cells, indicating that it may function as an autoreceptor (Helboe and Moller, 1999; Cristiani et al., 2000; Dal Monte et al., 2003b). Numerous evidence indicates that SRIF mediates its actions by interacting mainly with sst_2 receptors which, in the rabbit retina, couple to Goα (Vasilaki et al., 2003). Of the two sst_2 receptor isoforms, sst_{2A} receptor has been immunohistochemically localized in rat, rabbit and mouse retinas (Johnson et al., 1998, 1999; Helboe and Moller, 1999; Fontanesi et al., 2000; Petrucci et al., 2001; Vasilaki et al., 2001; Cristiani et al., 2002). In rabbits, it is expressed mainly by rod bipolar and by sparse amacrine cells. These amacrine cells have been reported to lack (Johnson et al., 1998) or only to partially express (Fontanesi et al., 2000) tyrosine hydroxylase (TH) immunoreactivity. In the rat retina, sst_{2A} receptor has been localized in amacrine cells, including TH-containing amacrine cells, in rod and cone bipolar cells and in horizontal cells (Johnson et al., 1999). The finding of sst_{2A} receptors expressed by bipolar cells is consistent with recent data demonstrating that SRIF may control the retinal release of glutamate through the activation of sst_2 receptors (Dal Monte et al., 2003a). This is also consistent with previous results reporting a SRIF-induced, sst_2 receptor-mediated down-regulation of Ca^{2+} influx in dissociated rod bipolar cells, thus providing evidence for an inhibitory feedback loop regulating transmitter release from rod bipolar cells (Petrucci et al., 2001). The sst_{2B} receptor isoform in the rat retina is predominantly found on the membrane of photoreceptors, indicating SRIF actions in the outer retina (Vasilaki et al., 2001). Finally, sst_4 receptor immunolabeling in mouse retinas is localized to sparse cells in the GCL that originate long process bundles in the NFL. These cells cannot be observed after optic nerve transection and they are therefore interpreted as ganglion cells (Cristiani et al., 2002).

Neuropeptide expression in developing mammalian retinas

Peptidergic systems that have been investigated with some detail in the developing mammalian retina include tachykinin peptides, SRIF, VIP, PACAP, NPY, opioid peptides and CRF.

Tachykinin peptides

In immunohistochemical studies, antibodies directed to SP are likely to also recognize neurokinin A and neurokinin B (Brecha et al., 1989), therefore we will refer to the reported immunolabeling as tachykinin immunoreactivity. Immunohistochemical methods have been employed to study the development of tachykinin peptide-containing cells in rabbit, rat and human retinas (Sakiyama et al., 1984; Nguyen-Legros et al., 1986; Yew et al., 1991; Zhang and Yeh, 1992; Jotwani et al., 1994; Casini et al., 1997b, 2000) and in the human retinogeniculate pathway (Wadhwa et al., 1988). In addition, there are reports of reduction in the number of tachykinin-containing amacrine cells in a guinea pig model of experimental growth retardation (Rees and Bainbridge, 1992), while no effects are detected in the development or survival of the tachykinin-immunostained amacrine cells following neonatal optic nerve transection (Osborne and Perry, 1985). In mammalian retinas, tachykinin immunoreactivity and tachykinin mRNA have been localized to mainly amacrine and displaced amacrine cells, with their processes arborizing at three distinct levels in the IPL. In addition, the presence of tachykinin immunoreactivity in ganglion cells of the rat and rabbit retina has been documented (see Casini et al., 1997b, 2002, for references).

In rat retinas, earlier investigations reported that tachykinin immunoreactivity could be first detected in amacrine cells at PND 4 or PND 5, while displaced amacrine cells in the GCL were detected later (Sakiyama

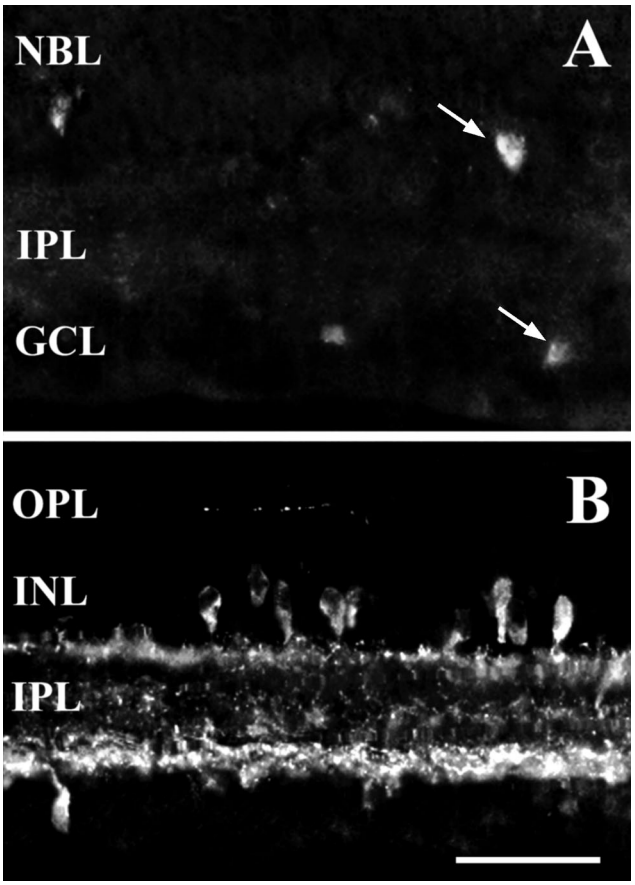


Fig. 3. Tachykinin immunofluorescence micrographs in sections through the thickness of rat retinas. Immunolabeled somata are detected at birth in the inner neuroblastic layer (NBL) and in the GCL (arrows in **A**). At eye opening (**B**), the immunostaining pattern is similar to that of adult retinas. Other abbreviations as in the text. Scale bar: 40 μm.

et al., 1984; Zhang and Yeh, 1992). More recent data, indicate that tachykinin-containing cells are already present in the newborn retina and that they are located both in the INL and in the GCL (Casini et al., 2000; Fig. 3). Interestingly, [^{3}H]-thymidine experiments indicate that the tachykinin-containing cells in the INL and those in the GCL constitute two separate groups that are generated in two distinct histogenetic waves during the time frame of amacrine cell birth (Zhang and Yeh, 1992). These studies also demonstrated that the cells in the INL begin detectable expression of tachykinin peptides 6-8 days after their birth, while the lag in tachykinin expression in cells of the GCL reaches 10 -12 days. Furthermore, since the number of immunostained cells both in the INL and in the GCL significantly increases over the first 3 postnatal weeks and mitotic activity is absent during this period, it can be hypothesized that several cells start the expression of the tachykinin phenotype over a relatively extended period of postnatal development (Zhang and Yeh, 1992). A similar observation has been reported in the development of dopaminergic amacrine cells of the rabbit retina (Casini and Brecha, 1992b), and it indicates two possible alternatives for the formation of amacrine cell populations characterized by a neurochemical phenotype: either (i) a number of cells are committed to a certain phenotype at the time of their birth but its expression is delayed over a long developmental period; or (ii) there are cells that are not committed but start expressing a particular phenotype under the influence of signals that become available in the microenvironment. Tachykinin peptides, presumably released by the first differentiated cells, may induce the expression or the acquisition of the same phenotype in other cells during the subsequent developmental period.

In the rabbit retina, tachykinin-immunolabeled cells are present in the GCL of the newborn retina, while immunostained cells in the INL are seen at PND 2 (Casini et al., 1997b), following a temporal pattern that is opposed to that observed in rat retinas, where tachykinin-containing cells in the INL seem to appear before those in the GCL (Sakiyama et al., 1984; Zhang and Yeh, 1992). In adult rabbit retinas, many of the tachykinin-containing cells in the GCL are ganglion cells (Brecha et al., 1987), and many of the tachykinin-immunolabeled cells in the GCL of developing retinas are also likely to be ganglion cells. Indeed, in newborn retinas heavily immunolabeled fiber bundles can be seen to run in the NFL and to converge into the optic disk (Casini et al., 1997b; Fig. 4). Both in rat and in rabbit retinas, the morphological development of the tachykinin-containing cells in the INL as well as in the GCL is completed by the time of eye opening (see Fig. 3; Sakiyama et al., 1984; Zhang and Yeh, 1992; Casini et al., 1997b).

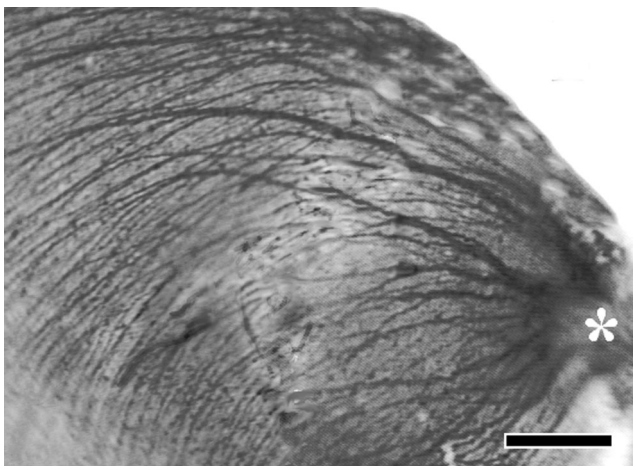


Fig. 4. Low power photomicrograph from a whole-mounted rabbit retina at PND 0 showing fiber bundles directed to the optic disk (asterisk) and probably representing tachykinin-immunolabeled ganglion cell axons. Scale bar: 150 μm.

In human retinas, tachykinin-containing cells have been identified, together with other neuroactive substances, at embryonic ages. There are discrepancies concerning the time of the first appearance of detectable levels of tachykinin immunoreactivity in retinal cells. An earlier investigation reported the first detection of tachykinin immunoreactivity in retinas of 24-29-week-old fetuses (Nguyen-Legros et al., 1986), while a more recent paper puts it at around 14 weeks (Jotwani et al., 1994). The earliest identification of tachykinin immunoreactivity in human retinas is reported in cells of the neuroblastic layer of 10-week-old fetuses, with subsequent development characterized by the migration of these cells into the inner layers of the retina (Yew et al., 1991). In addition, the presence of tachykinin immunoreactivity in optic nerves at 13-14 weeks of gestation indicates the presence of tachykinin-expressing ganglion cells in the developing human retina (Wadhwa et al., 1988).

Together, the studies of the localization of tachykinin peptides in developing mammalian retinas indicate that these peptides are expressed at early times of retinal maturation and roughly at the same time when other neurotransmitter systems begin their expression. The subsequent maturation of the tachykinin-containing cell populations follows a pattern that is similar to that of most amacrine cells and that is almost complete at the time of eye opening. SP and/or other tachykinin peptides presumably released in the developing retina may play a developmental role; however, it is difficult to hypothesize what kind of actions are performed by tachykinin peptides in developing retinas and whether these actions can be distinguished from those of other neuroactive substances that are present in the retina at the same time. An analysis of the expression of the neurokinin receptors in developing retinas may help to shed some light onto certain characteristics of the physiological actions of tachykinin peptides during retinal development.

Of the three neurokinin receptors, NK1 and NK3 are

present in the adult as well as in the developing rat retina, while NK2 is absent (Oyamada et al., 1999). The main finding about the developmental expression of NK1 and NK3 receptors in the rat retina is that NK1 receptors are expressed at early postnatal ages, while NK3 receptors appear only near the time of eye opening (Oyamada et al., 1999; Casini et al., 2000; Fig. 5), when the main morphological and functional characteristics of the retinal pathways have reached their maturity. These observations strongly suggest that SP may act at its preferred receptor (the NK1 receptor) in the retina during the whole period of postnatal development and therefore it may be implicated in developmental functions. In contrast, neurokinin B (the preferred ligand of NK3 receptors) could begin interactions with its receptors only when the retinal circuitry is almost ready to start the processing of visual stimuli, and developmental functions of neurokinin B and NK3 receptors seem unlikely.

In particular, NK1 receptors are expressed in the newborn retina by presumed ganglion cells and by a few amacrine cells in the neuroblastic layer. The subsequent development is characterized by substantial rearrangements of the NK1 expression patterns, which include an increase in the number of NK1-immunopositive amacrine cells, concomitant with a decrease in the number of immunolabeled presumed ganglion cells, and changes in the laminar distribution of NK1-immunostained fibers in the IPL. These fibers are first distributed to laminae 1, 3 and 5 of the IPL from PND 0 to PND 7, then they change to a pattern, seen at PND 12, where the most intensely immunolabeled part of the IPL is lamina 2, as in mature retinas (Casini et al., 2000). These findings, indicating profound changes in the expression patterns of NK1 receptors during retinal development, suggest that SP and NK1 receptors may mediate processes in the developing retina that are different from those in the retina capable of visual information processing.

NK3 receptors in adult rat and mouse retinas are expressed by populations of OFF-type cone bipolar cells (Oyamada et al., 1999; Casini et al., 2000; Haverkamp et al., 2003) and in dopaminergic amacrine cells (Chen et al., 2000). The same bipolar cells that express NK3 receptors can also be labeled with antibodies directed to the calcium binding protein recoverin (Casini et al., 2000; Haverkamp et al., 2003). A parallel immunohistochemical investigation of NK3 and recoverin immunolabelings in the developing rat retina indicated that recoverin-containing bipolar cells have reached an advanced degree of morphological maturation when they start expressing NK3 receptors, at a time just before eye opening (Casini et al., 2000; Fig. 5). This observation suggests that the timing of NK3 receptor expression is set to allow certain types of bipolar cells to initiate their functions in visual information processing, and that NK3 expression in these cells is not required for developmental functions.

Recent immunohistochemical investigations on the expression of NK1 receptors in developing rabbit retinas

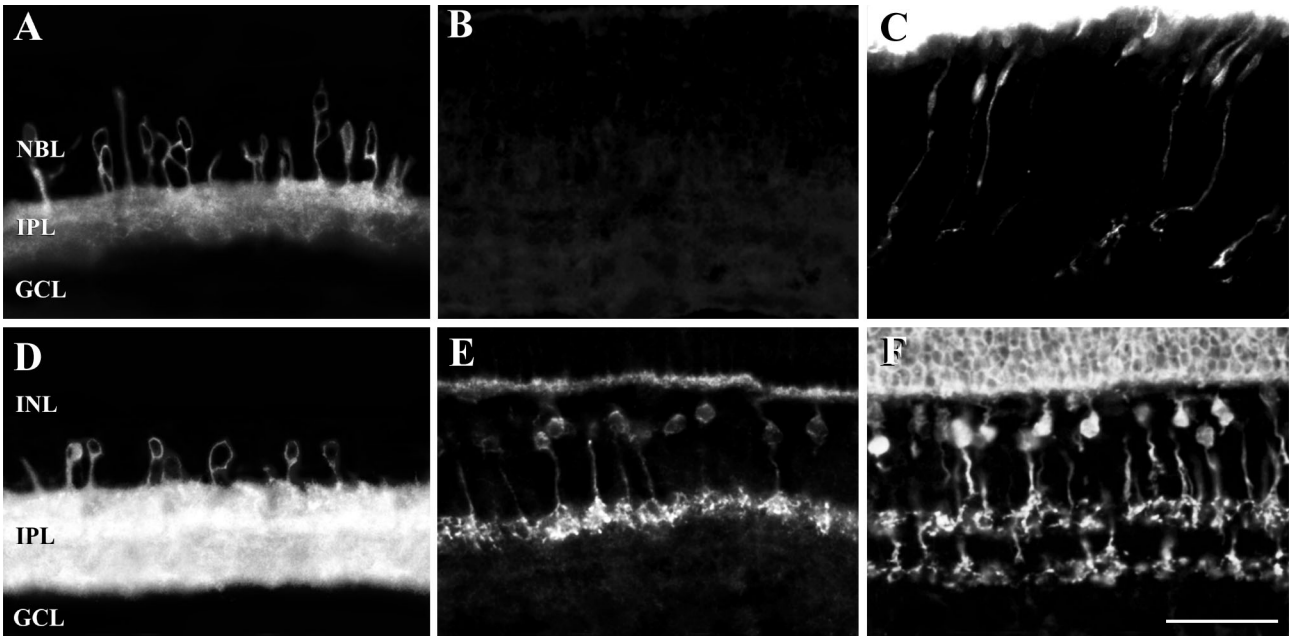


Fig. 5. Immunofluorescence micrographs in sections through the thickness of rat retinas at early postnatal ages **(A-C)** and at eye opening **(D-F)**. **A and D** are NK1-immunostained sections; **B and E** are NK3-immunostained sections; **C and F** are recoverin-immunostained sections. NK1 receptors are expressed early in the retina **(A)**, while NK3 receptors are first observed near eye opening **(E)**. Recoverin-immunolabeled bipolar cells are visible in the retina **(C)** when NK3 immunoreactivity is still undetectable. Refer to the text for further explanation. Scale bar: 40 μm.

seem to allow exciting new hypotheses on possible roles played by SP in the developing retina. As reported above, NK1 receptors in mature rabbit retinas are expressed by a population of ON-type cone bipolar cells and by the population of dopaminergic amacrine cells identified by tyrosine hydroxylase immunoreactivity (Casini et al., 2002). This adult pattern is achieved around the time of eye opening after a drastic rearrangement during the postnatal developmental period. In particular, before eye opening, NK1 receptors are expressed by cholinergic amacrine cells, while NK1 expression in dopaminergic amacrine cells and in bipolar cells is detected only at later ages (Casini et al., submitted; Fig. 6). Consistent with these immunocytochemical data, SP is ineffective in stimulating DA release in the developing retina, while it stimulates DA release in the mature retina (Casini et al., submitted). It is easy to hypothesize that this surprising switch in NK1 expression patterns may reflect substantial changes in the functional actions of SP. In particular, the onset of NK1 expression in dopaminergic amacrine cells and in a population of ON-type cone bipolar cells at eye opening indicates that this pattern is consistent with actions played by SP on vertical retinal pathways and on dopaminergic amacrine cells for visual information processing, probably including modulation of light adaptation (see Casini et al., 2002). In contrast, the expression of NK1 receptors by cholinergic amacrine cells in the immature retina is likely to be related to a role of SP in modulating cholinergic neurotransmission in the developing retina. Since cholinergic amacrine cells have been shown to directly participate in the spontaneous rhythmic activities in the developing rabbit retina (Zhou, 2001b; Feller, 2002), SP may be a factor implicated in the regulation of this important mechanism. Consistent with this hypothesis, SP or a SP agonist have been observed to increase the intracellular Ca^{2+} levels in individual cholinergic amacrine cells of the newborn rabbit retina (Casini et al., submitted).

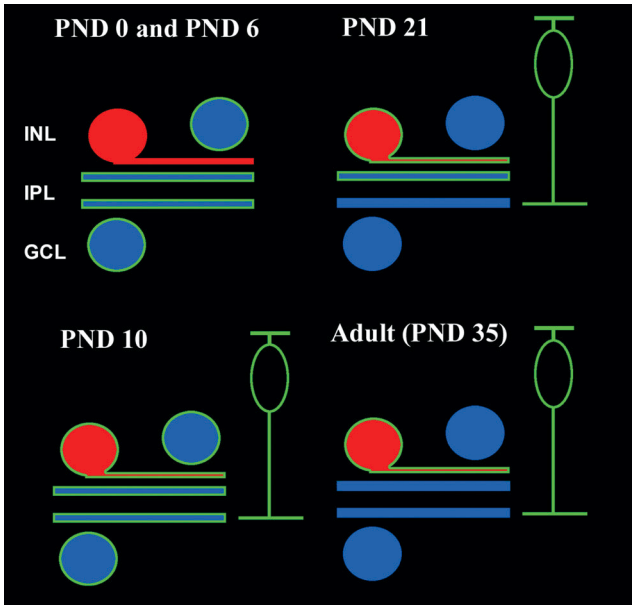


Fig. 6. Developmental expression of NK1 receptors in the rabbit retina as described in the text. Red indicates tyrosine hydroxylase immunoreactivity; blue indicates choline acetyltransferase immunoreactivity; green indicates NK1 receptors.

Somatostatin

As mentioned above, SRIF-14 is the predominant form of SRIF in most mammalian retinas. In adult retinas, SRIF immunoreactivity is localized to sparsely distributed, wide-field amacrine and displaced amacrine cells in the rat, guinea pig and human. In the rabbit, cat and primate retina, most SRIF immunoreactive cells are displaced amacrine cells, and they are predominantly distributed to ventral retinal regions. SRIF immunoreactivity has also been localized in a small percentage of ganglion cells in cat and monkey retinas (see Cristiani et al., 2002, for references).

The development of SRIF-containing cells has been investigated in a variety of mammalian retinas, including rat (Kirsch and Leonhardt, 1979; Ferriero and Sagar, 1987; Ferriero et al., 1990), rabbit (Brecha et al., 1991), guinea pig (Spira et al., 1984), and cat (Mitrofanis et al., 1989b; White and Chalupa, 1992). In human retinas there are also observations of the presence of SRIF-containing cells, mainly in the GCL on the 14^{th} or 15^{th} week of gestation (Mitrofanis et al., 1989b; Jen et al., 1994), with immunolabeled cells that are first observed in the central retina and which subsequently become restricted to ventral retinal regions (Mitrofanis et al., 1989b).

In rat retinas, the first SRIF immunoreactive cells appear in the neuroblastic layer as early as embryonic day 16 (Ferriero and Sagar, 1987). These cells are migrating neuroblasts that reach the GCL where they are homogeneously distributed at embryonic day 20. At birth, SRIF-containing cells are only localized in the GCL, while from PND 4 to PND 10 the number of immunostained cells increases in the INL and decreases in the GCL. During the same period, the processes of these cells grow into the IPL (Ferriero and Sagar, 1987). Radioimmunoassay studies show that SRIF is present in a very high concentration prenatally (10-fold higher concentration than in adults), while SRIF levels dramatically decrease soon after birth, and at PND 4 they amount to 14% of adult values. Subsequently, there is an increase until, by the time of eye opening, the amount of SRIF approaches adult levels (Ferriero and Sagar, 1987). A similar developmental pattern has been described for SRIF mRNA, suggesting that SRIF gene expression is controlled throughout development at the transcriptional level (Ferriero et al., 1990). Interestingly, the content of SRIF-28, which is virtually absent in adult retinas, is similar to that of SRIF-14 from embryonic day 19 to approximately PND 4, then it declines

considerably around eye opening time (Ferriero et al., 1990). These observations, indicating high levels of SRIF-14, SRIF-28 and SRIF mRNA at late prenatal/early postnatal periods strongly suggest a role of somatostatinergic transmission in retinal development.

In rabbit retinas, SRIF immunolabeled cells are first observed at embryonic day 25, which is about five days before birth, in small somata scattered throughout the INL of the ventral retina. These cells progressively migrate to the GCL, where they are exclusively localized at PND 4. SRIF immunoreactive processes invade specific IPL laminae to reach the adult pattern at eye opening (Brecha et al., 1991). An additional population of SRIF-containing cells, different from that of sparsely distributed displaced amacrine cells, is transiently present in the GCL from embryonic day 29 to PND 15-20. These cells are confined to the ventral retina and they are characterized by a lack of any immunostained processes. They are distributed in an apparently regular array with peak density in the central retina and lower density in the peripheral retina (Brecha et al., 1991). Although the significance of this transient population of SRIF-containing cells is unknown, their regular array indicates that they may serve as stable positional markers which may influence the direction of fiber outgrowth in the developing retina and/or the development of retinal mosaics.

In guinea pig retinas, different from other species, the predominant form of SRIF is SRIF-28. SRIF immunoreactive somata are only localized in far peripheral retinal regions in the INL, IPL and GCL, with fibers in the IPL and in the NFL. In addition, the observation of immunostained fibers in the optic nerve and disc suggests the presence of SRIF-containing ganglion cells (Spira et al., 1984). SRIF quantified by radioimmunoassay is detected as early as the 6th week of gestation (full term is 10 weeks). Immunohistochemically-detected SRIF-containing cells are seen at 2 weeks before birth, coincident with the period of the most rapid increase in SRIF levels determined with radioimmunoassay. At birth, SRIF levels amount to two-thirds of adult levels (Spira et al., 1984).

In adult cat retinas, SRIF-containing cells are represented by displaced amacrine and alpha ganglion cells that are mainly distributed to the ventral retina (White and Chalupa, 1991). During development, SRIF immunoreactivity is first detected at embryonic day 30 in cells located in the innermost part of the retina. These cells belong to the population of displaced amacrine cells. They are first located in central retinal regions, but soon their pattern of distribution undergoes a substantial remodeling and at embryonic day 38 these SRIF-immunoreactive cells are detected in retinal peripheral areas. At embryonic day 45, SRIF-containing displaced amacrine cells are located principally in the inferior half of the retina, as in adults (White and Chalupa, 1992). No further significant changes in this cell population are observed throughout postnatal development (Mitrofanis et al., 1989b; White and Chalupa, 1992). The first SRIF-immunostained alpha ganglion cells are detected at PND 5. From their earliest appearance, these cells are located principally in the inferior retina. Their number gradually increases over an extended period of postnatal development, and at PND 38 they are still 40-70% of the adult population. The postnatal period is also characterized by the development of a rich meshwork of SRIF-immunolabeled processes that extend in laminae 1, 3 and 5 of the IPL in all retinal regions (White and Chalupa, 1992).

Together, these studies indicate that in all mammalian retinas SRIF is expressed at early developmental times. In addition, in specific mammalian retinas there are marked changes in SRIF content, in the levels of expression of SRIF mRNA, in the presence of specific SRIF-containing cell populations or in the distribution patterns of SRIF-immunoreactive amacrine cells. However, the most intriguing characteristic of the development of the retinal somatostatinergic systems is perhaps the transient appearance of SRIF-containing ganglion cells which has been documented in rat (Fontanesi et al., 1997; Xiang et al., 2001) and cat (Mitrofanis et al., 1989b; White and Chalupa, 1992) retinas and which has been postulated in human retinas (Mitrofanis et al., 1989b). In the developing rat retina, most cells in the GCL express SRIF mRNA between embryonic days 13 and 21 (birth). The number of these cells rapidly decreases after birth until PND 20, when the distribution of SRIF mRNA-expressing cells in the GCL is similar to that of adults. Many, if not all, of these cells are ganglion cells, since SRIF immunoreactivity is observed in the optic chiasm, optic tract and lateral geniculate nucleus during the prenatal period (Xiang et al., 2001). Another period of transient expression of SRIF in ganglion cells of the rat retina has been identified between PND 7 and PND 14 (Fontanesi et al., 1997). A population of transient SRIF-immunoreactive ganglion cells has also been reported in the cat retina during prenatal and early postnatal development in the superior and inferior retina (Mitrofanis et al., 1989b; White and Chalupa, 1992). These cells were no longer detected at PND 38 (White and Chalupa, 1992). The disappearance of SRIF-expressing ganglion cells could be attributed to cell death that is normally present both in rat (Potts et al., 1982; Perry et al., 1983) and in cat (Williams et al., 1986) retinas during the early postnatal period. Alternatively, these cells may cease SRIF expression or reduce it to undetectable levels. The latter seems to be the most likely possibility to explain the disappearance of SRIF-containing ganglion cells in rat retinas after PND 14 (Fontanesi et al., 1997), which is after the period of maximum ganglion cell death (Potts et al., 1982; Perry et al., 1983). Whatever the causes of the transient presence of these ganglion cells, it is easy to hypothesize that SRIF expressed in these cells may play a role in the organization of the GCL and/or in the formation of retinofugal projections. For instance, in the rat retina the numerous SRIF mRNA-expressing

ganglion cells observed prenatally (Xiang et al., 2001) may influence the early outgrowth of ganglion cell projections, while the presence of SRIF-containing ganglion cells between PND 7 and PND 14 coincides with the time when mature retino-collicular projections are established (O'Leary et al., 1986) which is just before the time of maturation of retino-collicular synapses (Simon and O'Leary, 1992).

SRIF binding sites indicating the presence of functional somatostatin receptors are detected in the rat retina as early as embryonic day 15 (Ferriero, 1992) or 16 (Bodenant et al., 1991). Subsequently, their levels decrease considerably (Bodenant et al., 1991; Ferriero, 1992) to a minimum detected at PND 2 followed by a peak at PND 11 and by the achievement of adult levels at eye opening (Ferriero, 1992). These data show that the developmental pattern of SRIF receptor expression is coincident with that of SRIF mRNA and SRIF peptide.

Recent RT-PCR analysis of the developing mouse retina indicates that SRIF and all of its receptor mRNAs are expressed at birth (Fig. 7). In particular, at all postnatal ages, the levels of sst_2 mRNA are higher than those of sst_1 and similar to those of sst_4. In addition, the developmental patterns of SRIF and sst_2 mRNAs share some similarities, with a decrease in the first postnatal week followed by a moderate increase to adult levels

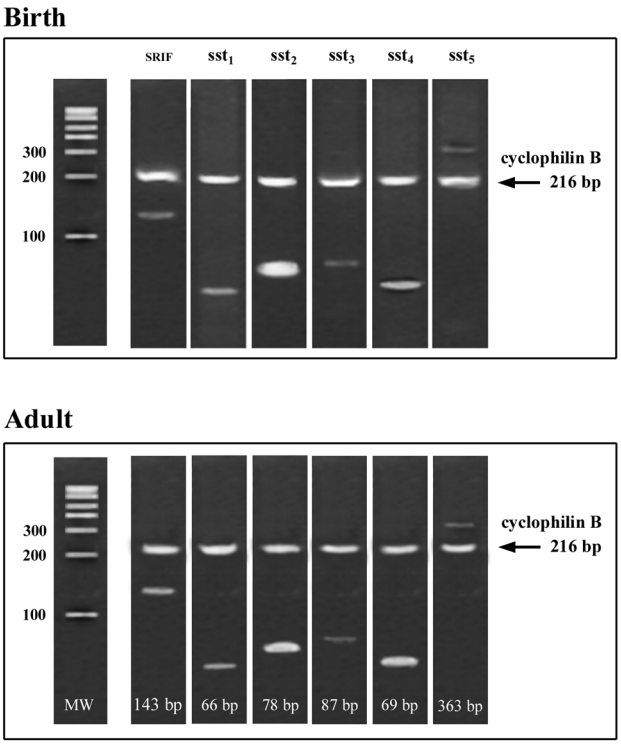


Fig. 7. Semiquantitative RT-PCR analysis of the expression of SRIF and its receptors in the newborn and in the adult mouse retina. Cyclophilin B mRNA was used as internal standard. All SRIF receptors are present, although in different amounts.

around the time of eye opening (Bagnoli P., unpublished observations). Immunocytochemically identified sst_1 receptors are detected in SRIF-containing displaced amacrine cells in the early postnatal retina (Bagnoli P., unpublished observations), indicating that, as in the adult retina (Cristiani et al., 2000), they may function as autoreceptors and control early SRIF release. Recent immunohistochemical studies have investigated the pattern of sst_{2A} receptor expression in the postnatal rabbit retina (Fontanesi et al., 2000). These receptors are present at birth and throughout postnatal development and they are localized in horizontal cells, rod bipolar cells and amacrine cells including TH immunoreactive amacrine cells, as in adult retinas. The adult pattern is reached at eye opening (Fontanesi et al., 2000). In the mouse retina, sst_{2A} expression by dopaminergic amacrine cells seems to precede that by rod bipolar cells (Bagnoli and Dal Monte unpublished observation).

The postnatal development of retinas of mice carrying genetic deletion of single SRIF receptors are under investigation by our group. Recent findings demonstrate major compensatory mechanisms induced by the deletion of sst_1 receptors (Dal Monte et al., 2003b). In particular, there is an increase in the levels of both SRIF and sst_2 receptor mRNA, indicating that sst_1 receptors may be involved in the regulation of both SRIF and sst_2 receptor expression. In addition, the increase of sst_2 receptor mRNA expression is accompanied by an increased expression of the sst_{2A} receptor isoform in rod bipolar cell axonal terminals, which is correlated with an increased size of rod bipolar cell axonal endings. These observations indicate that rod bipolar cell morphogenesis is affected by the deletion of the sst_1 receptor.

Vasoactive intestinal polypeptide

In mammalian retinas, VIP is localized in a population of wide-field amacrine cells and in a few displaced amacrine cells (see Lee et al., 2002, for references) which, in the rabbit retina, have been shown to constitute a subpopulation of GABAergic amacrine cells (Casini and Brecha, 1992c).

The development of VIP-containing amacrine cells has been investigated in rat retinas. In an earlier immunocytochemical study, VIP-immunoreactive amacrine cells were first observed at PND 12, which is 2 -3 days before eye opening (Terubayashi et al., 1982). However it seems likely that VIP expression in the rat retina appears within a few days after birth. Indeed, VIP immunoreactivity was detected in retinal cell cultures within 6 days after plating dissociated retinal cells from rats at embryonic day 19 (Fukuda et al., 1987), suggesting that, if developmental times in culture are similar to those *in vivo*, VIP-containing cells should appear around PND 5. More recent in situ hybridization studies confirmed that VIP mRNA is expressed in rat retinas at PND 5 (Casini et al., 1994). These cells appear to complete the migration to their final laminar position in the INL and in the GCL by the time of eye opening. In

addition, VIP-expressing amacrine cells are distributed in a fairly regular mosaic just before eye opening, suggesting they may efficiently influence all retinal regions at this time. A quantitative analysis of the VIP mRNA-expressing amacrine cells in postnatal rat retinas indicated that both cell density (labeled cells/mm^2 of retinal area) and total cell number peak at PND 15 (eye opening) and decrease to adult values in the following period (Casini et al., 1994). The increase in VIP mRNA-expressing cells is unlikely to be due to the addition of new cells, since mitotic activity in the rat retina ceases by PND 8 (Webster and Rowe, 1991), while the decrease in labeled cells after PND 15 cannot be ascribed to cell death among amacrine cells, since it has virtually ceased by PND 13 (Horsburgh and Sefton, 1987). It therefore appears that some amacrine cells may transiently express VIP during the time of eye opening. These observations suggest that VIP could act as an important factor during a specific period of retinal development when retinal pathways begin the processing of visual information. Other studies show that in retinal cell cultures derived from early postnatal rats, VIP protects retinal neurons from tetrodotoxin-induced death or from glutamate neurotoxicity, probably by stimulating cAMP production (Kaiser and Lipton, 1990; Shoge et al., 1998), indicating that VIP may behave as a growth or protecting factor for retinal cells in the developing retina. In addition, VIP possibly released by the retina and the choroid promotes the differentiation of a functional retinal pigment epithelium during development (Koh, 2000). Finally, studies in juvenile monkeys which had developed myopia after lid fusion due to excessive elongation of the eye reported that VIP immunohistochemical staining was much stronger in the closed than in the open eyes (Stone et al., 1988), suggesting that VIP may play a part in the regulation of postnatal ocular growth.

Together, these studies indicate potential roles of VIP in a variety of aspects of the development of the retina and of other ocular tissues, although specific actions exerted by this peptide have yet to be clarified.

Pituitary adenylate cyclase activating polypeptide

Only a few studies have investigated the presence of PACAP in developing retinas, but the findings indicate that it is expressed early in development. For instance, PACAP mRNA has been detected in the GCL of rat retinas at embryonic day 20 (Skoglosa et al., 1999), while RT-PCR and receptor-binding studies have reported the presence of PACAP and of PAC1, VPAC1 and VPAC2 receptors in retinas of 12-18-week human embryos (Olianas et al., 1997).

Similar to VIP, PACAP protects retinal neurons from cell death. In particular, administration of PACAP to retinal cell cultures from early postnatal rats increases the survival of different types of retinal cells counteracting anysomicin- or glutamate-induced cell death (Shoge et al., 1999; Silveira et al., 2002). In addition, it is demonstrated that the protective actions are mediated by PAC1 receptors through the intracellular cAMP/cAMP-dependent protein kinase pathway (Silveira et al., 2002). These findings indicate that PACAP may represent an important factor modulating cell death/survival in the developing retina.

Neuropeptide Y

In mammalian retinas, NPY immunoreactivity is localized in wide-field amacrine and displaced amacrine cells. In addition, it is also reported in ganglion cells of the cat and human retina (see Oh et al., 2002, for references).

In the human fetal retina, NPY immunopositive cells have been found as early as 14 or 15 weeks gestation in the INL (Jen et al., 1994; Jotwani et al., 1994), while by 17 weeks gestation, NPY-containing cells are also observed in the GCL (Jen et al., 1994).

In mouse retinas, RT-PCR data show that NPY expression does not vary between PND 7 and PND 17, while the expression of NPY receptor subtypes Y1 and Y2 increases from PND 7 to PND 12. Studies in a mouse model of oxygen-induced retinopathy suggest that NPY is involved in abnormal angiogenesis in retinopathy (Yoon et al., 2002).

In rat retinas, there are immunocytochemical observations showing that NPY-containing cells appear in the GCL at late prenatal ages. At PND 6, the first immunolabeled cells are observed in the INL and by PND 13, NPY-containing cell populations in the INL and in the GCL can be appreciated (Ferriero and Sagar, 1989). Radioimmunoassay measurements of NPY indicated a transient increase in NPY expression around PND 13, which is near eye opening (Ferriero and Sagar, 1989). A similar developmental pattern is found in mouse retinas, where a peak of NPY mRNA is recorded with semi-quantitative RT-PCR analysis at the time of

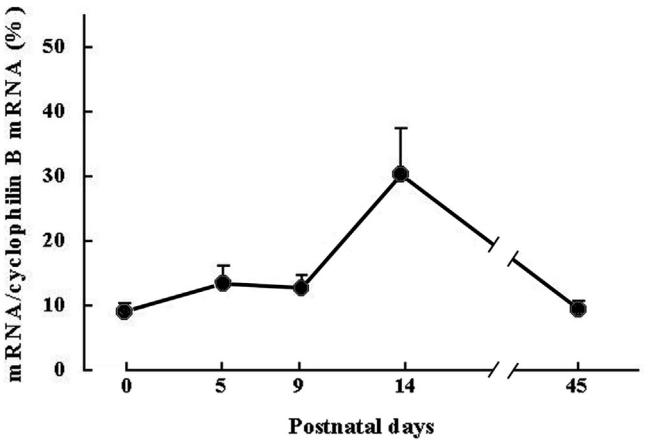


Fig. 8. Time course of NPY mRNA expression in the mouse retina as determined with RT-PCR semiquantitative analysis using cyclophilin B mRNA as internal standard. A significant, transient increase in NPY mRNA levels is observed at the time of eye opening ($P<0.01$).

eye opening (Bagnoli and Dal Monte unpublished observations; Fig. 8). The transient increase in NPY expression at eye opening suggests that this peptide may have a role at this time in modulating developing retinal circuitry.

In cat retinas, NPY-immunoreactive cells are first observed at embryonic day 46 in the GCL, while by embryonic day 50 they are also observed in the INL. Both the amacrine cell population in the INL and the ganglion cell group in the GCL (identified by retrograde labeling) initially follow a central to peripheral pattern of development. At PND 7 the number of amacrine cells approaches adult values, while the ganglion cell population shows a protracted development, with new cells being added until the third postnatal week. NPY-containing amacrine cells are regularly distributed throughout development, suggesting that they may participate in establishing the ganglion cell mosaics that appear during postnatal development (Hutsler and Chalupa, 1995).

Together, these data indicate that NPY is expressed in mammalian retinas roughly at the same time as other peptides and classical transmitters. Certain features of the NPY patterns in developing retinas may indicate some developmental roles for this peptide, however precise functions of NPY in retinal development are still unexplored.

Opioid peptides

Among mammalian retinas, opioid peptides, namely enkephalin peptides, have only been reported in guinea pig retinas, while μ receptors are likely to be expressed by rat and monkey ganglion cells (Wamsley et al., 1981; Altschuler et al., 1982).

In human retinas, enkephalin immunoreactivity is first observed at 16 or 17 weeks gestation (Yew et al., 1991; Jotwani et al., 1994). The following development occurs in a sequence from outer to inner layers of the developing retina (Yew et al., 1991).

Some papers in the nineties investigated both the localization and the growth factor function of enkephalin peptides in the developing rat retina (Isayama and Zagon, 1991; Isayama et al., 1991, 1995, 1996). Using immunocytochemistry, in situ hybridization, Northern blot, HPLC, and receptor binding, these studies reported the expression of [Met^5]-enkephalin, preproenkephalin (PPE) mRNA and [Met^5]-enkephalin binding sites in late prenatal/early postnatal rat retinas. In particular, [Met^5]-enkephalin-immunopositive and PPE mRNA-expressing cells are located in the neuroblastic layer and in the GCL of perinatal retinas. Immunolabeling and receptor binding are absent at PND 5-6 and in adult retinas, suggesting transient expression of [Met^5]-enkephalin and its receptor (Isayama et al., 1991, 1995), although PPE mRNA has also been localized in the INL of adult rat retinas (Isayama et al., 1996).

Regarding possible functional actions of [Met^5]-enkephalin in developing retinas, it is reported that this peptide significantly reduces the proportion of cells incorporating [^{3}H]-thymidine in PND 1 rat retinas. This effect is inhibited by the opioid antagonist naloxone, while the other antagonist naltrexone is capable of increasing [^{3}H]-thymidine incorporation (Isayama et al., 1991). These observations indicate that opioid peptides may serve during retinal development as negative regulators of cell proliferation.

Corticotropin releasing factor

In mammalian retinas, CRF immunoreactivity is localized in wide-field amacrine and displaced amacrine cells (Marshak, 1989; Yeh and Olschowka, 1989).

CRF-immunolabeled cells are detected in rat retinas at PND 3 located in the neuroblastic layer and in the GCL. They are first distributed in central retinal regions, then they are localized to other parts of the retina following a center-to-periphery pattern of expression, with progressive growth of immunolabeled processes into specific IPL laminae. The adult distribution is achieved at PND 13 (Zhang et al., 1990). The observation that CRF-containing cells in the INL decrease in number, while those in the GCL increase during postnatal development indicates that the final distribution in the INL and in the GCL is reached by virtue of a secondary migration of CRF-containing cells from INL to GCL (Zhang et al., 1990). Further studies using [^{3}H]-thymidine autoradiography showed that CRF-containing cells are generated between embryonic day 16-20, indicating a certain delay in the subsequent acquisition of the transmitter phenotype by these cells (Zhang and Yeh, 1991).

There are observations of transient changes in CRF expression indicating a possible importance of CRF during retinal development. Indeed, radioimmunoassay experiments suggest the presence of a peak in the expression of CRF in the retina around the time of eye opening (PND 15) (Zhang et al., 1990), which evokes the peaks in VIP and in NPY expression at the same time. In addition, immunohistochemistry combined with [^{3}H]-thymidine autoradiography indicates the presence of transient CRF horizontal cells that are generated at embryonic day 14-18. These cells, located in the distal neuroblastic layer/INL, decrease in number around PND 7-9 following a centro-peripheral pattern and they are no longer detected at PND 19 (Zhang and Yeh, 1991).

Concluding remarks

The mammalian retina represent a useful experimental model to investigate the characteristics of neuronal development and the factors that may be implicated in such processes. The ultimate aim of these research lines is to identify selected molecules that may be employed as therapeutic agents to treat damage and/or illness of the nervous system. Although major progress has been made in the field of neuropeptides, with identification and cloning of peptide receptors,

development of peptide-related drugs and production of transgenic animals, we are still very far from a knowledge of peptide functions in neuronal development that could allow the design of peptide-based therapeutic strategies. Nonetheless, the data reviewed in the present paper indicate that after a phase in which peptides and their receptors have been localized in developing retinas, some functional properties of peptides that may affect the development of retinal neurons are beginning to be clarified and that specific aspects of the development of peptidergic systems may start attracting attention for deeper investigation. For instance, the study of possible actions of SP for the modulation of cholinergic neurotransmission sustaining the retinal spontaneous waves of activity may lead to important discoveries concerning the involvement of tachykinin peptides in the formation of intraretinal pathways and of retinofugal projections. In addition, some aspects of the developmental patterns of the somatostatinergic system, including early SRIF expression, the presence of transient SRIF-expressing ganglion cells and observations in SRIF receptor knock-out mice, clearly indicate varied roles of this peptide in retinal development that deserve detailed investigations. Furthermore, the protective and growth-promoting actions of VIP and PACAP indicate that these peptides may act to sustain retinal neurons during their development. Finally, future investigations should also concentrate on the data showing a peak in the expression of certain peptides, including VIP, NPY and CRF, around the time of eye opening, when the retinal pathways achieve their final organization and start the analysis of structured visual information, suggesting that these peptides may operate, or co-operate, during this delicate phase of retinal development.

In summary, although the story of neuropeptides reveals itself to be much more complicated than it was thought when these neuroactive molecules were first identified, the results of the research done in the developing retina as well as in other models of the developing nervous system allow a certain degree of optimism for important achievements in the field of neuropeptides in the near future.

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