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Recent Research on the Centrifugal Visual System in Mammalian Species

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Abstract

Ample evidence indicates that both retinofugal (classical visual and the retino-hypothalamic pathways) and retinopetal connections (centrifugal visual system) are found between the eye and the central nervous system. More than hundred years ago Ramon Y Cajal and Dogiel, whose names are very well known by neuro-anatomists, described the termination pattern of the fibers deriving from the avian central nervous system. However, the location of nerve cell bodies was not known at that time. In the last century many data accumulated about these neurons not only in lower vertebrates but in mammals as well. The structures where the neurons give rise to the centrifugal visual fibres in mammals are the following: reticular formation and raphe nuclei of the midbrain, superior colliculus, pretectum, gray matter of the midbrain, dentate gyrus, CA1 and CA3 regions of the hippocampus, olfactory tubercle, habenula, indusium griseum, hypothalamic supraoptic, Paraiventricular and arcuate nuclei, and the lateral hypothalamus. The centrifugal visual fibers enter the optic nerve layer, then reach the inner plexiform layer and terminate in the inner nulear layer of the retina in the vicinity of the amacrine cells. A series of neuropeptides and neurotransmitters was described in the origin of the centrifugal visual system. These are the followings: luteinizing hormone releasing hormone, pituitary adenylate cyclase activating polypeptide, vasoactive intestinal polypeptide, serotonin, histamine and leu-enkephalin. Several hypotheses arose on the function of this system. Centrifugal visual system arising from the histaminergic mammillary neurons modifies the sleep/wake cycle. Hallucinogenic drugs through the limbic system may cause disturbance of visual function and result in seeing visual hallucinations or distorted images.

Keywords: Mammals; Rat; retina; Retinopetal fibers

Abbreviations

ARC: Arcuate Nucleus; BDA: Biotinylated Dextran Amine; CA1 and CA3: Regions of Hippocampus; CoL: Cobaltic Lysin; DAB: Diaminobenzidine Hydrochloride, DG: Dentate Gyrus; ECR: Ectopic Cell Region; FB: Fast Blue; FG: Fluoro-Gold; FMRF-amide: Amide Composed of Four Amino Acids (Phe-Met-Arg-Phe); GFP : Green Fluorescence Protein; HRP: Horseradish Peroxidase; INL: Inner Nuclear Layer; IPL: Inner Plexiform Layer; ION: Isthmo-optic Nucleus; L-ENK: Leu-enkephalin; LHRH: Luteinizing Hormone Releasing Hormone; OPL: Outer Plexiform Layer; PACAP: Pituitary Adenylate Cyclase Activating Polypeptide; PhA-L: Phaseolus Vulgaris Leucoagglutinin; PVN: Paraventricular Nucleus; SCG: Superior Cervical Ganglion; SCN: Suprachiasmatic Nucleus; SON: Supraoptic Nucleus; VIP: Vasoactive Intestinal Polypeptide; WGA: Weat Germ Agglutinin

Introduction

It is well known that the ganglion cells of the retina send fibers to the lateral geniculate body which is an intermediate center of the visual pathway. Scharrer [1] hypothetized that photic stimuli from the eye are conducted not only to the main visual centers, but also to some hypothalamic neurons, and then to neuroendocrine effector cells. He called this system the photoneuroendocrine one. The anatomical basis of this system, the retinohypothalamic tract was later discovered [2,3]. The main retinorecipient area of the hypothalamus is the suprachiasmatic nucleus (SCN) which regulates biological rhythms [4]. It is also called "biological clock" or "mind's clock" [5].

Reverse connections (centrifugal visual system, retinopetal fibers) between the central nervous system and the retina were first described by Cajal [6] and Dogiel [7] in avian retina and optic nerve. Later it became evident that this system is generally present in vertebrates [8-10] including some mammals such as monkey, cat [11] and human [12-14]. Several structures were proposed to be the origin of these fibers: the reticular formation of the brain stem [15], the superior colliculus [16] and the lateral geniculate nucleus [17]. A decade ago the intracerebral location of the retinopetal neurons, the mode of intra-retinal arborisations of the centrifugal fibres and the nature of their targets, their neurochemical properties, and the afferent supplies of these neurons were summarized by Reperant et al. [18]. They have stated that the centrifugal visual system is not a homogeneous entity formed by neurons with a common embryological origin, but rather a collection of at least eight distinct subsystems arising in very different regions of the neuraxis. These are the following: the olfacto-retinal, dorsal thalamo-retinal, ventral thalamo-retinal, pretecto-retinal, tecto-retinal, tegmento-mesencephalo-retinal, dorsal isthmo-retinal and ventral isthmo-retinal systems. The olfacto-retinal system, which is probably absent in Agnatha (jawless fish), appears to be a pleisiomorphic characteristic of all Gnathostomata (all vertebrates with upper and lower jaws), while the tegmento-mesencephalo-retinal system appears to be present only in Agnatha. It was supposed that the different above-mentioned retinopetal pathways were selected on the basis of widely different environmental pressures. The review mainly deals with data concerning the non-mammalian species. We have an effort to concentrate to the mammalian centrifugal visual system.

Neurons Sending Efferent to Mammalian Retina

Several regions of the mammalian central nervous system, where retinopetal fibers arise from, were previously demonstrated. Itaya and Itaya [19] described retinopetal fibers originating from the medial pretectal area and periaqueuctal gray matter of rats. Several other researchers also supposed the presence of hypothalamoretinal connections in mammals. After administering fast blue (FB) into the vitreous body labeled cells were found in the SCN and the anteromedial region of the arcuate nucleus (ARC) of a primate, Microcebus murinus (grey mouse lemur) [20]. Horse-radish peroxidase (HRP) injected into the vitreous body resulted in the appearance of labeled perikarya in the ventral hypothalamus of dogs [21].

We have observed vasoactive intestinal polypeptide (VIP) immunoreactive fibers leaving the suprachiasmatic and above lying regions and entering into the optic nerves as it were observed in sagittal sections of the rat hypothalamus. These VIP fibers exhibit a characteristic pattern. They form bilateral bundles in the dorsal part of the optic chiasm rostral to the SCN and they spread out like a fan into the optic nerves. With the use of enucleation (removal of eyes) or colchicine administration into the eye, VIP immunoreactive cell bodies were demonstrated in the supraoptic (SON) and paraventricular nuclei (PVN) which were not seen in intact rats. Iontophoretic administration of the phaseolus vulgaris leucoagglutinin (PhA-L) into the SON and PVN resulted in the appearance of PhA-L containing fibers in the optic nerve. These findings indicate that VIP fibers observed in the optic chiasm and the optic nerve may originate from the hypothalamus [22]. About three decades ago several cobalt complex labelling of neural pathways was widely used for light and electron microscopic investigations [23]. It was found that within two days this improved tracer is transported up to 40-50 mm distance from the applied site [24]. In our other experiment an improved cobaltic lysin (CoL) containing polyethylene tube was applied to the rostral end of the cut optic nerve. The end of the tube was sealed. Cobalt containing nerve cell bodies appeared in the SON, the PVN and the mammillary region (our unpublished data) (Figure 1 A-C). These results supported the previous hypothesis that in rats some neurons of the hypothalamus also send fibers to the retina. The following experiments carried out in our laboratory unequivocally certify the above-mentioned hypothesis [25]. The most critical step was to choose suitable tracer for demonstrating retrogradely labelled neurons. It had to fulfil the following criteria:

1. Not to pass through the wall of vessels.

2. Not to pass through synapses.

3. Not to pass through gap junctions.

4. To be small enough for the transportation by thin, delicate fibers.

It has been known for a long time that the centrifugal visual system is composed of very thin fibers which are unmyelinated and their number varies in different species, 10 vs. 10000 in human and chicken, respectively [18]. We utilized the retrograde transport of biotinylated dextran amine (BDA 10,000 MW) injected into the vitreous body and the anterograde transport of an iontophoretically applied tracer Fluoro-Gold (FG) to the location where the majority of the labeled cells was expected. BDA and FG were visualized using ABC immunoperoxidase method and nickel intensification of diaminobenzidine tetrahydrochloride (DAB) reaction as described previously [26,27]. It was found that BDA injected into the vitreous body of the eye of rats resulted in a considerable number of retrogradely labeled nerve cell bodies, besides the SON and the PVN, in many structures such as the dentate gyrus (DG), CA1 and CA3 regions of the hippocampus, the habenular complex, the indusium griseum, mammillary region and the olfactory tubercle. The labelling appeared in all the three layers of DG: molecular, granule and polymorph layers. In CA1 and CA3 regions the labeled cells were mainly in the pyramidal cell layer. The injection of tracer to one eye resulted in cell body labeling at both sides of the forebrain. Counting the labeled cells it was found that the number of these cells in the ipsilateral hippocampal formation was 618 ± 177, at the contralateral side 877 ± 391. It seems that all together about 1500 neurons from the hippocampal formation and at least similar number of neurons in other regions (olfactory tubercle, SON, PVN, mammillary region, habenular complex, indusium griseum, pretectum) send fibers to the retina when the tracer is injected into one eye. Figure 1D shows fibers in the optic nerve. Some fibers are very delicate. These may compose the retinohypothalamic pathway and the others may be the centrifugal visual fibers. Figure 1E shows fine fiber-network in the SCN, the main termination of the retinohypothalamic tract. Perikarya were never labeled in this nucleus indicating that the tracer did not pass synapses. Figures 1F-1K shows BDA labeled neurons in several characteristic places.

In lower vertebrates (reptiles) the pineal organ is the parietal eye. The parietal eye is a part of the epithalamus which can be divided into two major parts: the epiphysis (the pineal organ, or pineal body if mostly endocrine) and the parietal organ (often called the parietal eye, or third eye if it is photoreceptive). The parietal eye is the wavelength discriminator; however, the two in the front of the head are responsible for image-forming color vision [28]. In mammals the remnant of this double organ, the pineal body functions as an endocrine organ. It is mainly composed of pinealocytes which secrete melatonin in a circadian rhythm. The highest melatonin level occurs during the night time [29]. During darkness, the SCN sends a neural impulse to the PVN, from where fibers descend to the intermediolateral cell columns and then the superior cervical ganglion (SCG) which innervates the pineal body with noradrenergic fibers. The above mentioned neural impulse from SCG causes the discharge of norepinephrine from the postganglionic terminals near the pinealocytes. The catecholamine acts primarily on conventional β-adrenergic receptors on the pinealocyte membranes; this action culminates in a series of molecular events that induce the night-related rise in pineal melatonin synthesis and release [30].

Eldred and Nolte [31] demonstrated that in the pineal body of vertebrates photoreceptor molecules (visual pigment) are also present. Extracranial pineal organs of submammalians are cone-dominated photoreceptors sensitive to different wavelengths of light, while intracranial pineal organs predominantly contain rod-like photoreceptor cells. These latter photoreceptor molecules are responsible for the perinatal entrainment of rhythmic functions in mammals. Later in adult life the sympathetic nervous system takes over this task [32].

As mentioned above it was accepted for a long time that between the eye and the pinealocytes there is only retinofugal neuronal connection composed of at least 5 neurons [33]. In several species including humans [34], cotton rats [35] and monkeys [36] the pineal body contains neurons. Recently, it was demonstrated in our laboratory that the pineal neurons in hamsters send information through a multisynaptic pathway to the retina [37]. Exclusively

retrogradely transported transneuronal spreading virus was injected into the vitreous body of rats and golden hamsters. The virus expressed green fluorescence protein (GFP) and in this way it was readily detectable under fluorescence microscope. Four days later GFP containing neuronal cell bodies were found in the pineal body of 2/13 rats. In both cases only one cell was seen in the whole organ (all sections were mounted and investigated). However, in hamsters we always found many viruses labelled cell bodies (5-36/organ). The localization was characteristic. The nerve cell bodies were mainly, but not exclusively, seen in the central region of the organ (Figure 1L).

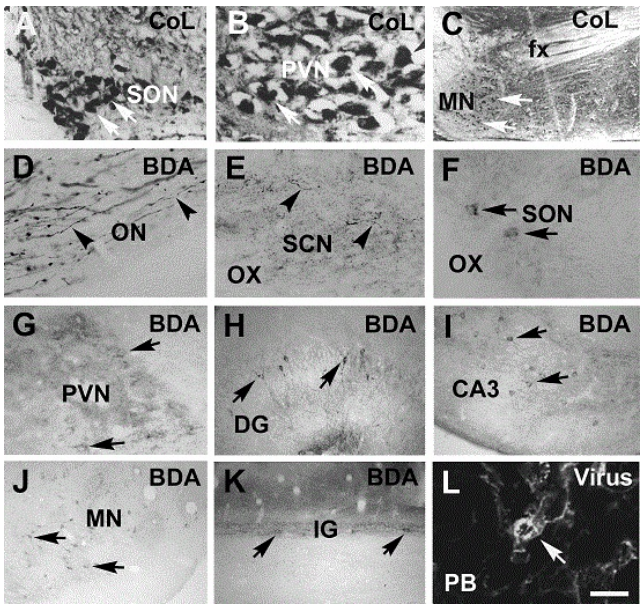

Figure 1: Microphotographs showing labelled neurons in the forebrain and the PB of rats after intravitreous injection of CoL, BDA or retrograde spreading virus expressing GFP. In A-B CoL labeled perikarya are seen in the SON, PVN and MM nuclei. D and E show BDA labelled fibers in the ON and the SCN. The delicate fibers in the ON may be the centrifugal visual ones or the components of the retinohypothalamic tracts. F-K show BDA labelled cell bodies in the SON, the PVN, the DG, the CA3 region, MN and IG. L shows a virus labelled neuron in the pineal body. Arrows indicate perikarya and arrowheads indicate fibers. Abbreviations: BDA: Biotinylated Dextran Amine; CA3: Region of the Hippocampus; CoL: Cobaltic Lysin; DG: Dentate Gyrus; fx: Fornix; IG: Indusium Griseum; MN: Mammillary Nuclei; ON: Optic Nerve; OX: Optic Chiasm; PB: Pineal Body; PVN: Hypothalamic Paraventricular Nucleus; SCN: Suprachiasmatic Nucleus; SON: Supraoptic Nucleus. Scale bar: 30 µm in L; 50 µm in B, D and E; 75 µm in A and F; 100 µm in G-I and K; 200 µm in C and J.

Chemical Coding of Retinopetal Fibers

Several neuropeptides are candidates for influencing the retinal function via the centrifugal visual system in mammals. In the optic nerve, optic chiasm and optic tract of the adult rat luteinizing hormone-releasing hormone (LHRH) fibers were first demonstrated by Santacana et al. [38]. In our laboratory VIP fibers were observed in the optic tract and optic chiasm. These fibers persisted three months after enucleation indicating their origin in the central nervous system [22]. Pituitary adenylate activating polypeptide (PACAP) in the optic nerve was also observed [25]. These fibers may come from the PACAP immunoreactive ganglion cells. Collaterals of these neurons participate in the formation of the retinohypothalamic tract [39,40]. Double labelling of the neurons, which contained BDA after the administration of the tracer into the vitreous body, revealed the presence of BDA in VIP immunoreactive cells of the DG, but not in the CA1 or CA3 regions of the hippocampus. BDA appeared in LHRH immunoreactive cells of the DG, the indusium griseum and the olfactory tubercle and it also appeared in PACAP immunoreactive cells of the DG, the SON and the medial habenula. Rusoff and Hendrickson [41] investigated the retinae of a monkey, cat, rat and mouse and did not find FMRF-amide immunoreactivity, a marker for efferent fibers in the retinae of lower vertebrates. Therefore, they concluded that efferent fibers are immunologically different from efferent fibers in lower vertebrates where FMRF amide was usually observed.

In an early study Moore and Sibony [34] found leu-enkephalin (L-ENK) immunoreactive nerve cell bodies in human pineal body. The neurons had extensive dendritic arborization and immunoreactive axons were present in the septae and beneath the capsule, particularly in a perivascular location, and occasionally extended into lobules of the organ among parenchymal cells. Unfortunatelly in human there is no possibility to verify whether these cells give rise to the pinealo-retinal pathway.

Villar et al. [42] using HRP injection into the posterior chamber of the eye of rats found labelled polygonal, ovoid, fusiform and small multipolar neurons in the lateral cell groups of the dorsal raphe nucleus. Several days later a very small electrolytic lesions of this region produced a significant decrease in the serotonin content of the retina measured by high-performance liquid chromatography. These results demonstrate the existence of a centrifugal projection from the lateral cell groups of the dorsal raphe nucleus to the retina and show its probable serotonergic nature.

In this moment there is no information about the chemical nature of the neurons locating in the pineal body and giving rise to the pinealo-retinal pathway.

Finally with the use of electrophysiological approach it was demonstrated that the two mammalian eyes communicate directly with each other via the optic nerve. The crosstalk alters the retinal activity in rats and perhaps in other animals as well [43].

Termination of Retinopetal Fibers

It has generally been accepted for more than a hundred years that there are centrifugal fibers in the retina arising in the central nervous system. There are only a small number of these retinopetal axons, but their branches in the inner retina are very extensive. Unfortunately the majority of data concerning the termination of the centrifugal visual fibers in the retina are derived from birds.

Birds: The major source of these fibers is the isthmo-optic nucleus [44]. Two basic types of the centrifugal visual fibers were described: convergent and divergent [45,46]. The fibers derived from the isthmo-optic nucleus (ION) and the surrounding ectopic cell regions (ECR) of the pigeon brain were traced to the retina [47]. It was found that the ECR gives rise only to the divergent type of the centrifugal fibers, whereas the ION gives rise mainly to the convergent type but may also send some fibers of the divergent type. Most of the fibers project

contralaterally, although a few from the ECR project ipsilaterally. The terminals of either type are not uniformly distributed throughout the retina; instead, they are found mainly in the inferior, midtemporal, to nasal portion of the retina and appear to avoid the fovea and most of the red field. The authors supposed that the centrifugal axons act by increasing the gain on the accessory optic system, thereby enhancing retinal stabilization of gaze with improved accuracy of pecking of small objects. Nickla et al. [48] showed that cytochrome-oxidase histochemistry in chicken retina specifically labels convergent centrifugal axons and target neurons which appear to be amacrine cells, as well as three types of ganglion cells: two types found in the inner nuclear layer (INL) (displaced ganglion cells) and one in the ganglion cell layer. Labeled target amacrine cells have distinct darkly labeled nests of boutons enveloping the somas. They are associated with labelled centrifugal fibers, and are confined to central retina. Lesions of the isthmo-optic tract abolish the cytochrome-oxidase labelling in the centrifugal axons and in the target amacrine cells but not in the ganglion cells. Cytochrome-oxidase-labelled ganglion cells in the INL are large; one type is oval and similar to the classical displaced ganglion cells of Dogiel, which have been reported to receive centrifugal input. The other type is rounded.

Mammals: Iontophoretic injections of PHA-L into the oculomotor nucleus of rats resulted in labelling of retinopetal fibers which reach the eye via the optic tract and optic nerve. Preterminal arborizations were found in the INL of the retina. In addition, labeled fibers have been observed which seemed to terminate within the optic tract and optic nerve. It is suggested that the projection from the oculomotor nucleus to the retina constitutes a link in the multisynaptic efferent pathway from the visual cortex to the eye, by which the visual cortex can influence the function of the retina [49].

Gastinger et al. [50] summarized the data concerning the termination of centrifugal visual fibers in mammalian retinae. Three types of retinopetal axons are described. The first type gives rise to terminals in the outer zone of the IPL. These fibers have been identified in dog [21] and chimpanzee retinae [16]. The second type of retinopetal axons is larger in diameter, varicose, and terminates in the outer plexiform layer (OPL). In rats, these axons are labelled with antibodies to serotonin. The third type of retinopetal axon branches extensively in IPL. With the use of the Golgi method, Polyak [16] described axons like these in macaque retinae. They run in the optic fiber layer (OFL), and they give off a nearly vertical branch to the IPL, where they branch extensively in a broad band in the center of the layer. It was also demonstrated that serotonin is released from retinopetal axons. Physiological data carried out in rabbits [51] suggest that serotonin released from retinopetal axons improves the performance of neural circuits in the retina at scotopic or mesopic levels of illumination, the conditions prevailing when these animals are awake. Serotonin would be expected to increase absolute sensitivity of rabbit retinal ganglion cells by decreasing surrounding inhibition. Serotonin also increases the responses to increments in light intensity in cat and rabbit retinal ganglion cells, probably through its effects on bipolar cells. Serotonin increases the sensitivity of ganglion cells to light stimuli in dark-adapted rabbit retinae. Serotonin also inhibits dopamine release from amacrine cells. This may contribute to dark adaptation.

According to Gastinger et al. [50] the third type of centrifugal visual fibers can be stained for histamin immunoreactivity in guinea pigs and macaque retinae. These histaminergic fibers are derived from the tuberomammillary region, the only place where histaminergic neurons are present in mammalian nervous system [52]. Application of HRP to the proximal end of cut optic nerve resulted in HRP labelled neuronal cell bodies in this region [53]. The histaminergic neurons that project to the retina are a subset of the "waking-on" neurons found in the tuber mammillary nucleus of the posterior hypothalamus of rats [54] and cats [55,56]. The release of histamine in the retina varies according to the sleep/wake cycle of the animal. Histamine is expected to be released from retinopetal axons during the day in diurnal animals and during the night in nocturnal animals. While GABA [57,58], glutamate, NO [59] and acetylcholine [48] are involved in the function of the centrifugal visual system in sub-mammalian species, these transmitters are not described in mammals.

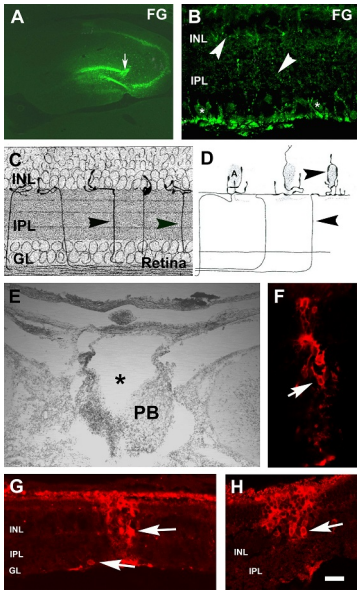

Figure 2: Microphotographs demonstrating the termination of centrifugal visual fibers in rats. A shows the place of the iontophoretic application of FG tracer into DG (indicated by a small arrow). B demonstrates FG labelled fibers in the retina (indicated by arrowheads). Asterisks show ganglion cells surrounded by centrifugal fibers. C and D show schematic drawings after Ramon y Cajal and Dogiel on the termination of centrifugal visual fibers in the avian retina (indicated by arrowheads). E shows the place of the anterograde virus administration into the PB in a golden hamster. Asterisk shows the injection site. F-H show virus labeled cell columns in the retina of the same hamster (indicated by arrows). Abbreviations: AC: Amacrine Cell; FG: Fluoro-Gold; GL: Ganglion Cell Layer; INL: Inner Nuclear Layer; IPL: Inner Plexiform Layer; PB: Pineal Body. Scale bar: 25 μm in B; 50 μm in F-H; 250 μm in A and E.

In our material the majority of the neurons giving rise to the centrifugal visual fibers in the rat were present in the DG [25]. That is why we administered FG tracer iontophoretically into the DG (Figure 2A), and looked for FG labelled fibers in the retina. The labelled fibers first appeared in the optic nerve layer, then traversing the layer of ganglion cells, they entered the internal plexiform layer (IPL). A few fibers reached the INL as well. In this layer they sometimes formed loops around unlabelled cells (Figure 2B).

Labelled ganglion cells were not seen in these animals. It was very impressive that the retinal distribution of FG labelled fibers was very similar to that pattern which was demonstrated by Cajal [60] and later by other researches in birds (Figures 2C and 2D). They described large calyx synapse between efferent fibers and the assotiation amacrine cells.

It seems that the labelled fibers in our material surround amacrine cells. Amacrine cells are interneurons in the INL interposed between bipolar and ganglion cells on one side and centrifugal fibers on the other side.

The pinealo-retinal connection is a multisynaptic pathway. Injection of anterograde spreading virus in the pineal body (Figure 2E) 5 days later appeared in the retina [37]. Labelled fibers were seen on the dorsal aspect of the optic nerve. The nerve cell bodies were arranged in columns in the retina (Figures 2F-2H). The columns contained amacrin cells, bipolar cells and ganglion cells. The distribution of the labelled columns in the retina is not mapped at this moment and we have no information about their functional significance.

Figure 3 schematically illustrates the morphology of the centrifugal visual system in mammals. Tables 1 and 2 summarize the data available in the literature on this system.

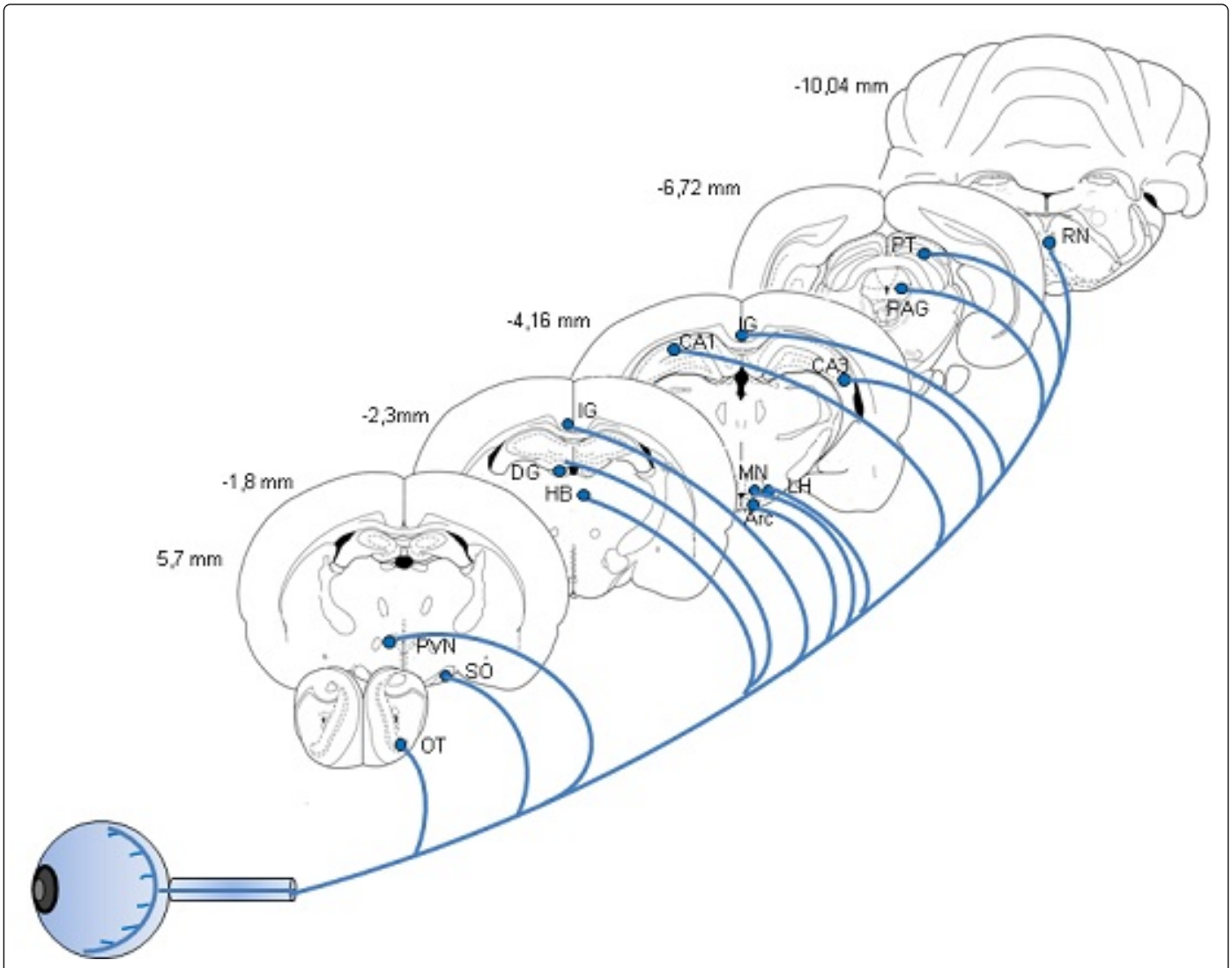

Figure 3: Schematic illustration showing the localization of the neurons giving rise to one-neural centrifugal visual pathways. This is a summary of the data based on our results and those available in the literature. The frontal sections derive from the atlas of Rat brain in stereotaxic coordinates (Paxinos and Watson, 2005). The numbers beside the sections indicate the distance in mm from the bregma. Abbreviations: ARC: arcuate nucleus; CA1 and CA3: Regions of the Hippocampus; DG: Dentate Gyrus; HB: Habenula; IG: Indusium Griseum; LH: Lateral Hypothalamus; MN: Mammillary Nuclei; OT: Optic Tract; PAG: Periaqueductal Gray Matter; PT: Pretectum; PVN: Paraventricular Nucleus; RN: Raphe Nuclei; SON: Supraoptic Nucleus.

Structure	Species	Tracer	Site of termination	Peptide or transmitter	References
FOREBRAIN					
Olfactory Tubercle	Rat	BDA		LHRH	Vereczki et al. (2006)
Mediolateral Preoptic Area	Rat	5,7-dihydroxytryptamine	OPL		Schütte, (1995)
Son, Pvn	Rat	CoL			unpublished data
	Rat	PhA-L		VIP	Fogel et al. (1996)
	Rat	BDA		PACAP	Vereczki et al. (2006)
Scn, Arc	Monkey	FB			Bons and Petter (1986)
Ventral Hypothalamus	Dog	HRP	IPL		Terubayashi et al. (1983)
Posterior And Premamillary Area Of Hypothalamus	Monkey, cat and guinea pig	HRP			Labandeira-Garcia et al. (1990)
	Macaque		IPL	histamin	Gastinger et al. (1999)
Dorsal Hypothalamus	Monkey	HRP			Labandeira-Garcia et al. (1990)
Dentate Gyrus, Induseum Griseum	Rat	BDA	INL	VIP, PACAP LHRH	Vereczki et al. (2006)
Ca1, Ca3,	Rat	BDA			Vereczki et al. (2006)
Habenular Complex	Rat	BDA		PACAP	Vereczki et al. (2006)

Table 1: Papers available in the literature on the localization of the neurons giving rise to the centrifugal visual system in mammalian forebrain.

Structure	Species	Tracer	Transmitter	References
BRAIN STEM				
Mesencephalon				
Lateral Geniculate Nucleus	Mongolian gerbil	HRP or WGA-HRP		Larsen and Moller, (1985)
Oculomotor Nucleus	Rat	NY		Hoogland et al. (1985)
	Rat	HRP		Labandeira-Garcia, (1988)
Central Gray Matter	Rat	HRP		Labandeira-Garcia, (1988)
Trochlear Nucleus	Rat	HRP		Labandeira-Garcia, (1988)
Laterodorsal Tegmentum, Lateroventral Tegmentum	Rat and rabbit, monkey, cat and rabbit	HRP		Labandeira-Garcia et al. (1990)
Pretectal Area	Rat	HRP		Itaya, (1980) Labandeira-Garcia (1988)
	Rat	BDA		Vereczki et al. (2006)
Medial Pretectal Area	Rat	WGA-HRP, FB, NY		Itaya and Itaya (1985)
	Rat, guinea pig	HRP		Labandeira-Garcia et al. (1990)
Medulla Oblongata				
Dorsal Raphe Nucleus	Monkey, cat and guinea - pig	HRP		Labandeira-Garcia et al. (1990)

	Rat	HRP	serotonin	Villar et al. (1987)

Table 2: Papers available in the literature on the localization of the neurons giving rise to the centrifugal visual system in mammalian brain stem.

Functional Considerations

The most studied structure is the ION of avian brain. This structure modifies the activity of the retina. It plays some role in the synthesis of visual focal attention. ION-lesioned chicks showed delay in pecking time to scattered grains [61]. In the early postnatal period unilateral disruption of centrifugal efferent to the retina of the contralateral eye from the ION induces an initial axial hyperopia, which is subsequently reversed through increased vitreous elongation in the affected eyes [62]. Centrifugal fibers arising in the Edinger-Westfal nucleus are responsible for visual acuity [49]. After the lesion of the tecto-fugal pathway there is deficit in the color reversal-learning [63,64]. The retinopetal pathway arising in the serotoninergic raphe nuclei can enhance phase shift of the circadian rhythm to light [51]. The histaminergic neurons that project to the retina are a subset of the "waking-on" neurons found in the tuber mammillary nucleus of the posterior hypothalamus [54-56]. Wirsig-Wiechmann and Wiechmann [65] did not find LHRH fibers in the vole retina but they could find LHRH receptor mRNA. This finding supports the view that LHRH has the potential of modulating visual processing in the retina of mammals as well, as already demonstrated in fish. The role of LHRH in white perch (fish) was studied by Umino and Dowling [66]. It was found that LHRH acts by stimulating the release of dopamine from interplexiform cells, depolarizing horizontal cells and increasing their responses to small spots while decreasing their responses to full-field lights.

There is evidence that retinal fibers terminate in the limbic system, in the thalamic nuclei and in the bed nucleus of stria terminalis [61]. Based on our findings that limbic structures (hippocampal formation, DG, Tu, IG, habenular comlex, SON, PVN nuclei of hypothalamus) send fibers to the retina, we proposed that there is a retino-limbic-retinal circuit through which light cues influence emotional behavior and neuroendocrine functions. Also, like a feedback mechanism, the limbic system influences intrinsic retinal signal transmission. The connections may be present between retinorecipient areas and limbic structures. This could be the reason why hallucinogenic drugs (LSD, Ecstasy) which can influence learning mechanisms through the hippocampal formation, might cause disturbance of visual function and result in seeing visual hallucinations or distorted images. These hallucinations could be due not only to the disturbed function of visual centers but also to the change in the sensitivity of the retina to light. This change in sensitivity could be influenced by the centrifugal visual fibers from the limbic system and could result in a faulty perception of the real world.

At this moment there is no direct evidence for the role of pineal-retinal pathways. We suppose, if this system exists in hamsters, it may be present in other mammals, where there are neuronal cell bodies in the PB.

Acknowledgement

All authors have equally contributed to the paper.

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