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Review

The nucleus isthmi and dual modulation of the receptive field of tectal neurons in non-mammals

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Abstract

The nucleus isthmi in the dorsolateral tectum had been one of the most obscure structures in the nonmammalian midbrain for eight decades. Recent studies have shown that this nucleus and its mammalian homologue, the parabigeminal nucleus, are all visual centers, which receive information from the ipsilateral tectum and project back either ipsilaterally or bilaterally depending on species, but not an auditory center as suggested before. On the other hand, the isthmo-tectal pathways exert dual, both excitatory and inhibitory, actions on tectal cells in amphibians and reptiles. In birds, the magnocellular and parvocellular subdivisions of this nucleus produce excitatory and inhibitory effects on tectal cells, respectively. The excitatory pathway is mediated by glutamatergic synapses with AMPA and NMDA receptors and/or cholinergic synapses with muscarinic receptors, whereas the inhibitory pathway is mediated by GABAergic synapses via GABA_A receptors. Further studies have shown that the magnocellular and parvocellular subdivisions can differentially modulate the excitatory and inhibitory regions of the receptive field of tectal neurons, respectively. Both the positive and the negative feedback pathways may work together in a winner-take-all manner, so that the animal could attend to only one of several competing visual targets simultaneously present in the visual field. Some behavioral tests seem to be consistent with this hypothesis. The present review indicates that the tecto-isthmic system in birds is an excellent model for further studying tectal modulation and possibly winner-take-all mechanisms.

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Abbreviations: AChE, acetylcholinesterase; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ChAT, choline acetyltransferase; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CPP, 3-*RS*-2-Carboxypiperazin-4-yl-propyl-1-phosphonic acid; ERF, excitatory receptive field; GABA, gamma-aminobutyric acid; Imc, the nucleus isthmi pars magnocellularis; Ipc, the nucleus isthmi pars parvocellularis; IRF, inhibitory receptive field; NI, the nucleus isthmi; NMDA, *N*-methyl-D-aspartate; Slu, the nucleus isthmi pars semilunaris or nucleus semilunaris

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The nucleus isthmi (NI) as a conspicuous paired mid-brain structure was first described in 1897 in amphibians by Gaupp; it is now found in all classes of nonmammalian vertebrates [97] and is assumed to be homologous to the parabigeminal nucleus in mammals [10,27,58,81] (Fig. 1). Previously, it had been suggested that this nucleus might be the midbrain representative of the auditory system [56,57]. However, neither auditory nor visual responses were recorded from the amphibian NI in 1965 [71]. Since the 1970s, the isthmic complex in a variety of species has been extensively studied neuroanatomically, electrophysiologically and behaviorally. The present review provides a relatively brief summary of multidisciplinary evidence that NI and its mammalian homologue are all visual centers, which can modulate the visual activity of tectal neurons in nonmammals. In birds, the magnocellular and parvocellular components of NI can modulate the excitatory center and inhibitory surround of the receptive field of tectal cells, respectively. It suggests that the isthmic complex may play an essential role in a winner-take-all network.

1. The nucleus isthmi and its mammalian homologue are visual centers

1.1. Cytoarchitecture and neural connections of the nucleus isthmi

The nucleus isthmi in anuran amphibians is a kidney-shaped structure located at the border between the mesencephalic tegmentum and cerebellum. It is divided into a cell-dense cortex peripherally and cell-sparse medulla internally, with a cell-free band (neuropil) medioventrally (Fig. 2A). The average number of NI cells in frogs is 7900 [101] and that in toads is 4800 [102]. Cortical cells could be classified into five types and most of them have piriform perikarya, whereas medullary cells of seven types mostly are piriform, fusiform, or multipolar in somatic shape [88]. In salamanders, NI has a shell-like shape, rostral to which is a neuropil formed by isthmic dendrites and axons of the tectoisthmic and isthmotectal tracts [118]. The isthmic neurons possess a piriform soma with an

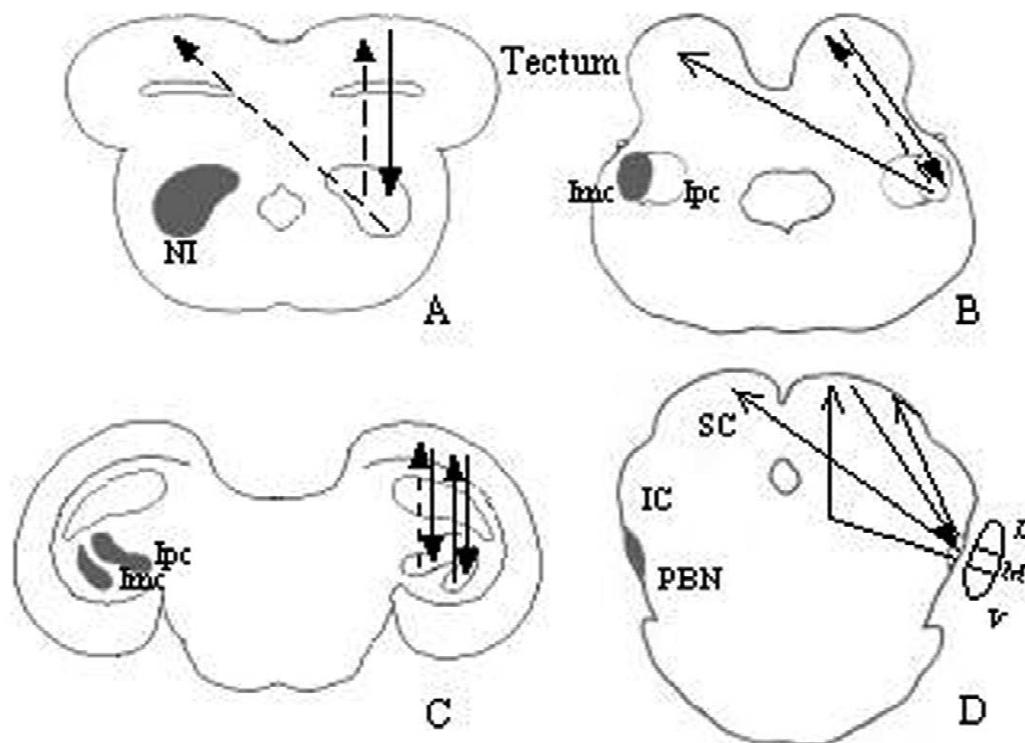


Fig. 1. Schematic cross-sections of midbrains showing neuronal pathways between the optic tectum and isthmic nuclei. The nucleus isthmi (NI) in frogs (A), the nucleus isthmi pars magnocellularis (Imc) in geckoes (B), Imc and the nucleus isthmi pars parvocellularis (Ipc) in pigeons (C), as well as the parabigeminal nucleus (PBN) in rats (D) all receive input from the ipsilateral tectum or superior colliculus (SC), and project back ipsilaterally (C) or bilaterally (A, B, D). Note that neuronal pathways between tectum and Imc via the nucleus profundus mesencephali in lizards (B) and those between tectum and the nucleus isthmi pars semilunaris in birds (C) are not drawn for clarity. The rat PBN (D) is divided into three subdivisions (D, M, V in inset), with dorsal and ventral divisions projecting back ipsilaterally and middle contralaterally. Thick arrows represent pathways electrophysiologically identified and thin arrows those not physiologically identified yet. Thick solid, dotted, and broken arrows signify excitatory, inhibitory and dual (excitatory and inhibitory) pathways, respectively. Based on Refs. [23,49,100–106,108,127].

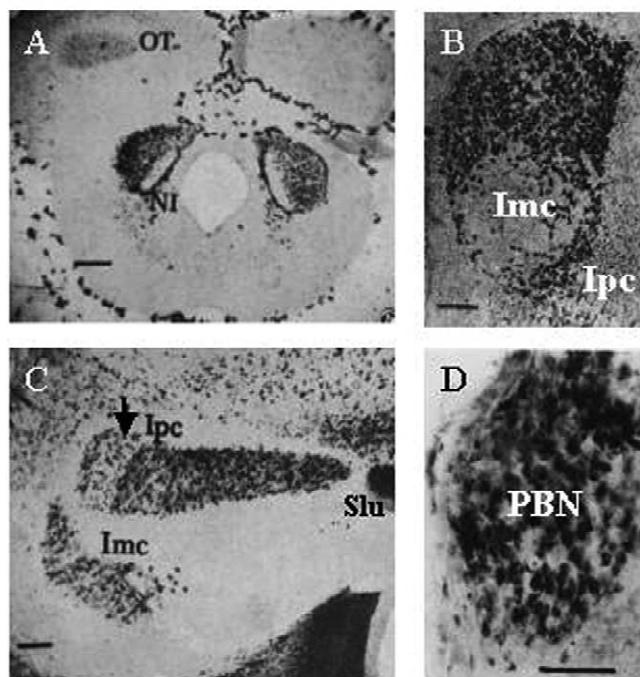


Fig. 2. Microphotographs showing cytoarchitecture of the nucleus isthmi (NI) in frogs (A), the nucleus isthmi pars magnocellularis (Imc) in geckoes (B), Imc and the nucleus isthmi pars parvocellularis (Ipc) in pigeons (C), as well as the parabigeminal nucleus (PBN) in mice (D). Isthmic neurons in non-mammals are stained for acetylcholinesterase and parabigeminal neurons in mammals for choline acetyltransferase. Note that NI in frogs is characterized by a cell-free band (neuropil) medioventrally. In geckoes, Imc but not Ipc cells are stained, with an inhomogeneous distribution of cells. The nucleus isthmi pars semilunaris (Slu) stained for acetylcholinesterase in C is just partially shown. Arrow in C points to an area where acetylcholinesterase staining is significantly reduced by tectal lesion. The anatomical locations of these nuclei are shown in Fig. 1. Dorsal is up, medial is to the right. Scales: 250 μm in A, C; 70 μm in B; 240 μm in D. Based on Refs. [60,67,104].

apical dendrite that extends rostralaterally and arborizes in the neuropil [117]. Dye coupling occurs between isthmic cells, probably indicating the existence of electrical synapses in the amphibian NI [117,124]. Interestingly, there may exist dye coupling between isthmic and tectal neurons in salamanders [117]. The isthmic nucleus receives input from the ipsilateral tectum and projects back ipsilaterally in teleosts [46,47,76,93,] but not [77], or bilaterally in amphibians [25,28,30,52,61,88,110,111,117–119] and in reptiles [54,103]. In anurans, the anterior nonrim cortex and the rostral medulla project to the ipsilateral tectum, whereas a band of cells in the middle medulla and most cells in the rim cortex project to the contralateral tectum [88]. However, the isthmo-tectal pathway in tongue-projecting salamanders is substantially different from that in other amphibians, showing that the majority of isthmic neurons project to both tecta [117]. In addition, the amphibian NI also receives input from the anterodorsal tegmental nucleus [92,123,125].

The isthmic complex in lizards is divided into two

subnuclei, the nucleus isthmi pars magnocellularis (Imc) and the nucleus isthmi pars parvocellularis (Ipc) (Fig. 2B). Their cells could be categorized into three types according to their dendritic patterns: (i) monopolar cells have piriform perikarya giving off an apical dendrite; (ii) bipolar cells possess polygonal or fusiform perikarya with two dendrites spreading out in the opposite directions or at certain angles; and (iii) multipolar cells are characterized by polygonal or spherical perikarya that radiate several dendrites [128]. Imc not only has connections with both tecta, but also receives input from and projects to the nucleus profundus mesencephali that is reciprocally connected with the ipsilateral tectum [103]. The isthmic complex in turtles consists of three cytoarchitecturally distinct nuclei: the rostral and caudal magnocellular nucleus isthmi, and the parvocellular nucleus isthmi [78]. The rostral magnocellular nucleus isthmi is identified as the nucleus profundus mesencephali in lizards [103], which is characterized by a loose group of neurons with elongated perikarya [78]. The caudal magnocellular nucleus isthmi and the parvocellular nucleus isthmi are equivalent to Imc and Ipc in lizards, respectively. They have reciprocal connections with the ipsilateral tectum, with Ipc additionally receiving input from the ipsilateral Imc and projecting to the contralateral tectum [54].

It has been generally accepted that the isthmic complex in birds consists of Imc, Ipc, and the nucleus isthmi pars semilunaris (also named the nucleus semilunaris, Slu) (Fig. 2C); the isthmo-optic nucleus is excluded because it projects centrifugally to the contralateral retina [91]. In pigeons, Imc neurons show a great variability in size (12–50 μm in diameter) of perikarya with several dendrites mostly bearing spines, whereas Ipc cells have round perikarya (about 20 μm) giving off a few thin and sparsely branching dendrites mostly being free of spines. Slu cells possess round-shaped perikarya (20 μm) having a few sparsely branching dendrites with mushroom-shaped spines [35]. Intracellular staining reveals dye coupling between Slu cells in about 22% of the cases examined on brain slices [Tang and Wang, unpublished data]. Both Ipc and Slu have reciprocal and topographic connections with the ipsilateral tectum [36,39,42,45]; Imc may receive tectal input [42,116] and project back ipsilaterally [85–87,112], and some Imc axons' collaterals may also project to Ipc as well [86].

The mammalian homologue of the nonmammalian NI is assumed to be the parabigeminal nucleus [10,27,58,81], which lies along the lateral wall of the midbrain just ventral to the brachium of the inferior colliculus (Fig. 2D). It is cytoarchitecturally divided into the dorsal, middle and ventral divisions in rats and golden hamsters [49,84], but not in the opossum [66]. The dorsal and ventral divisions are composed of fusiform cells, whereas the middle division is mainly formed of rounded or polygonal cells [84]. This nucleus receives input from the ipsilateral

superior colliculus and projects back bilaterally [2,27,49,51,54,66,81,115]. In particular, the dorsal and ventral divisions of the rat parabigeminal nucleus project to the ipsilateral tectum and the middle division projects to the contralateral tectum [49]. This nucleus is also connected with the dorsal lateral geniculate nucleus [10,37,38,90], as well as with the pulvinar nucleus and the central lateral nucleus [10]. Neurons in the isthmic nuclei in amphibians [60,64,79,96], reptiles [72,104] and birds [39,45,60,114], as well as those of the parabigeminal nucleus in mammals [3,67] share a common chemoarchitectural feature, i.e., they are stained for acetylcholinesterase (AChE) and choline acetyltransferase (ChAT) (Fig. 2). It appears that the isthmotectal pathways are cholinergic.

1.2. Visual response properties of isthmic neurons

Electrophysiological studies have shown that NI in teleost fish [69,120] and in amphibians [31,95,100–102,117,118], and both Ipc and Imc in birds [110,127] are all visual centers. Visual-auditory and multimodal units are found outside of the nucleus [102,103,127]. Only NI in a weakly electric fish receives electrosensory input in addition to visual afferents [77]. Histochemical and electrophysiological approaches have indicated that Imc and Ipc in lizards may be structurally and functionally independent, with Imc being a visual center [103]. This is not the case with the turtle NI, whose Imc and Ipc are reciprocally connected with the ipsilateral tectum and Ipc additionally receives input from the ipsilateral Imc and projects back to the contralateral tectum [54]. Two neuronal loops constitute the relation between tectum and Imc in lizards: a direct tectum–Imc–tectum loop, and an indirect tectum–nucleus profundus mesencephali–Imc–nucleus profundus mesencephali–tectum loop [103]. A similar indirect pathway is also found in teleost fish, which projects from tectum to NI via the nucleus pretectalis [47,93]. These indirect pathways may finally exert an inhibitory action on isthmic cells [47,103]. The parabigeminal nucleus in mammals is also a visual center that receives visual information from the ipsilateral tectum and projects back bilaterally [80–82].

Isthmic neurons in various species of animals examined so far share several visual properties: (i) they vigorously respond to motion of a small stimulus, usually preferring motion in the temporonasal direction; (ii) a retinotopic map exists in the isthmic nucleus and it registers with the visual field map in tectum; (iii) some isthmic neurons in non-avian vertebrates can be driven by either eye; and (iv) the isthmic nucleus receives input from the ipsilateral tectum and projects back either bilaterally or ipsilaterally. A comparison of the visual response properties of isthmic cells and those of tectal cells suggests that little information processing occurs in the isthmic nucleus [81,82,118]. Therefore, the nucleus has been thought as a

relay station, which conveys visual information from the contralateral eye to the contralateral tectum [25,28,30,88]. However, this hypothesis is challenged by three facts. First, some isthmic neurons already receive binocular inputs [80,101,118,119], and a substantial amount of optic axons directly project to the ipsilateral tectum in salamanders [73], implying that NI not only relays ipsilateral information but also might be involved in calculating three-dimensional trajectories of fast-moving objects [118,119]. Second, electrical stimulation of the toad NI could elicit excitatory (22%) and inhibitory (78%) responses in neurons intracellularly recorded from the contralateral tectum [108]. This finding is in accordance with lesion studies indicating that removal of isthmic input results in global disinhibition in bilateral tecta [25]. Double-labeling studies have shown that 62% of contralaterally projecting isthmic neurons is immunostained for gamma-aminobutyric acid (GABA) [62]. It appears that NI in amphibians may play an important role not only in relaying ipsilateral information but also with respect to inhibitory interactions between both hemispheres. Third, well developed Ipc and Imc in birds do not project to the contralateral tectum, indicating that both Ipc and Imc may modulate tectal activity rather than relaying ipsilateral information. As stated below, Imc and Ipc in birds can modulate tectal activity in excitatory and inhibitory ways, respectively [106,109].

1.3. Tecto-isthmic transmission is mediated by acetylcholine and glutamate

Neurotransmission from tectum to NI in amphibians is mediated by acetylcholine via muscarinic receptors, because atropine completely blocks isthmic responses to microiontophoretically applied acetylcholine and greatly decreases isthmic activity evoked by visual stimulation through tectum [14]. This finding is in agreement with histochemical studies showing the presence of high levels of AChE [60,79,99] and ChAT [64] in the amphibian NI. Tectal lesions result in the reduction or elimination of AChE staining within NI in a topographical manner [60], suggesting that at least some tectoisthmic fibers are cholinergic. In the pigeon, both Ipc and Imc are stained for AChE [45,60] and ChAT [114]. Tectal lesions result in the topographical disappearance of AChE staining within Ipc but not within Imc [45,60]. This could be explained by the possibilities that electrolytic lesions are made in a tectal region where no tecto–Imc projecting neurons exist, or tecto–Imc fibers are not cholinergic. The latter possibility, however, seems to be discrepant with the finding that neurons in Ipc and Imc are equally excited by acetylcholine, but the excitatory effect of *N*-methyl-D-aspartate (NMDA) is predominantly confined to Ipc. Firing activity of Ipc cells induced by NMDA is specifically blocked by CPP, an antagonist to NMDA [122]. It presumes that the tecto–Imc pathway may be cholinergic, whereas tecto–Ipc

fibers may be cholinergic and/or glutamatergic. Another possibility might be that glutamatergic receptors on Ipc cells mediate the synaptic transmission between both subnuclei, because Imc cells may give off axon collaterals to Ipc cells [86]. These differential sensitivities of Ipc and Imc cells to acetylcholine and NMDA enable an experimental strategy, in which different chemical substances (acetylcholine and NMDA) can be used to separately excite Ipc and Imc neurons for studying effects of isthmic excitation on tectal cells [109]. All these findings clearly show that the tectoisthmic pathways are excitatory and mediated by acetylcholine and/or glutamate as putative transmitters.

2. Modulation of tectal neurons by the isthmo-tectal pathways

2.1. Dual actions of NI on tectal neurons in amphibians and reptiles

In recent years, our great efforts have focused on the functional actions of isthmic cells on tectal neurons in amphibians, reptiles and birds. Electrical stimulation of NI in amphibians and Imc in reptiles produces excitatory and inhibitory postsynaptic potentials in tectal cells [23,105] (Fig. 3). These dual actions of isthmic stimulation on tectal activity are confirmed by subsequent microiontophoretic studies [126] (Fig. 4). In toads, isthmic stimulation could

exert an excitatory action on 80% of tectal cells, with mediation of acetylcholine and muscarinic receptors, and an inhibitory action on 20% of tectal cells through GABAergic synapses mediated by GABA_A receptors. In addition, visual responses in most tectal cells can be blocked by CPP, showing that retinotectal neurotransmission in amphibians is mainly mediated by glutamate via NMDA receptors. Some proportion of optic axons may use acetylcholine as a transmitter in retinotectal transmission mediated by muscarinic receptors. Taken together, retinal and isthmic afferents onto tectal cells converge in several combinations (Fig. 5). Tectal cells with cholinergic isthmo-tectal synapses receive either glutamatergic or cholinergic inputs from the retina, tectal cells receiving both cholinergic and indirect GABAergic afferents make either glutamatergic or cholinergic synapses with retinal afferents, and tectal cells make both GABAergic synapses with isthmo-tectal terminals and glutamatergic synapses with retinotectal terminals. This finding is supported by the fact that the isthmo-tectal pathway contains both cholinergic [60,75,96,104] and GABAergic fibers [61,62]. This cholinergic input from NI to tectum may be excitatory [17]. At least two groups of isthmic cells are stained for AChE [60,104] and GABA [61,62,70]. In addition, glutamate [7,21,40,68] and/or acetylcholine [18,24] may be involved in retinotectal transmission in amphibians. Within the tectum, a high density of both nicotinic and muscarinic receptors [18,19], as well as glutamate binding sites can be found in the superficial layers [7].

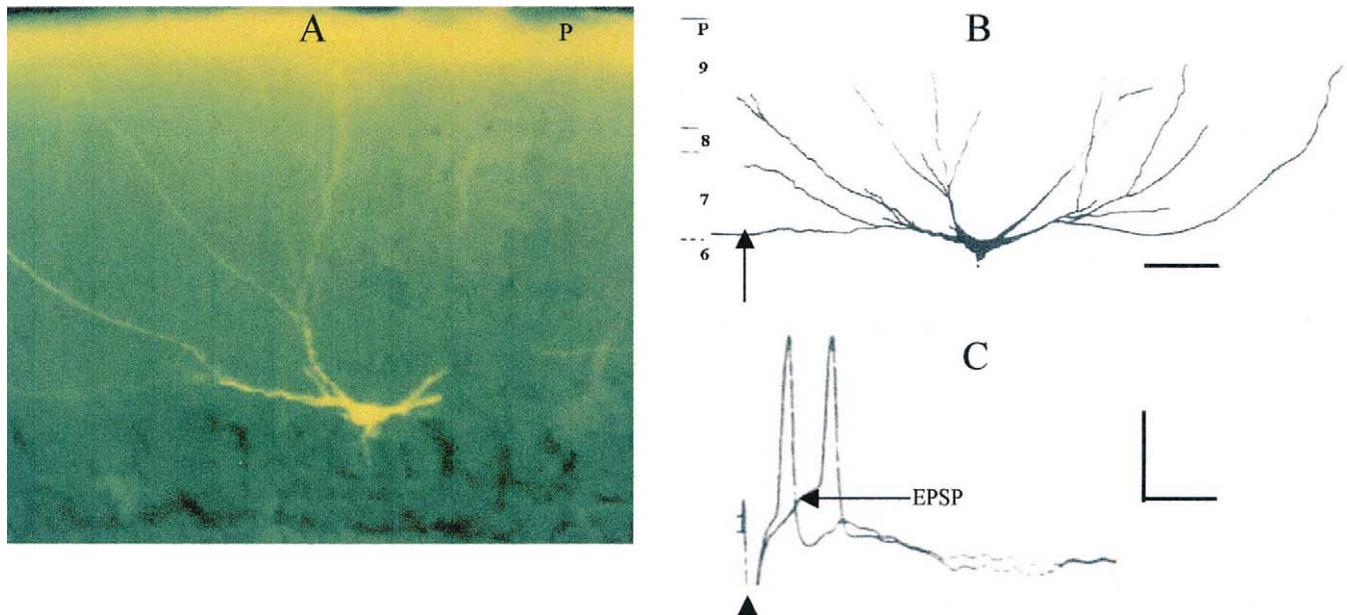


Fig. 3. Cellular morphology (A, B) labeled with Lucifer yellow and intracellular recordings (C) of a tectal neuron responding to electrical stimulation of the bullfrog nucleus isthmi. Microphotograph is taken from one of the cross-sections of tectum, with some dendrites (truncated) being in other sections (A). The morphology of this cell is graphically reconstructed based on the photomicrographs taken from the sections at different depths (B). This tectal cell responds to isthmic stimulation in an excitatory manner, with spikes riding on excitatory postsynaptic potentials (EPSP). Two superimposed sweeps. Letter P in A and B indicates the pia matter. Numerals in B show the tectal laminations. Thick arrow points to an axon, thin arrow EPSP, and arrowhead electrical stimulation artifacts. Scales: 100 μ m in B; 10 ms, 10 mV in C. Based on Ref. [105].

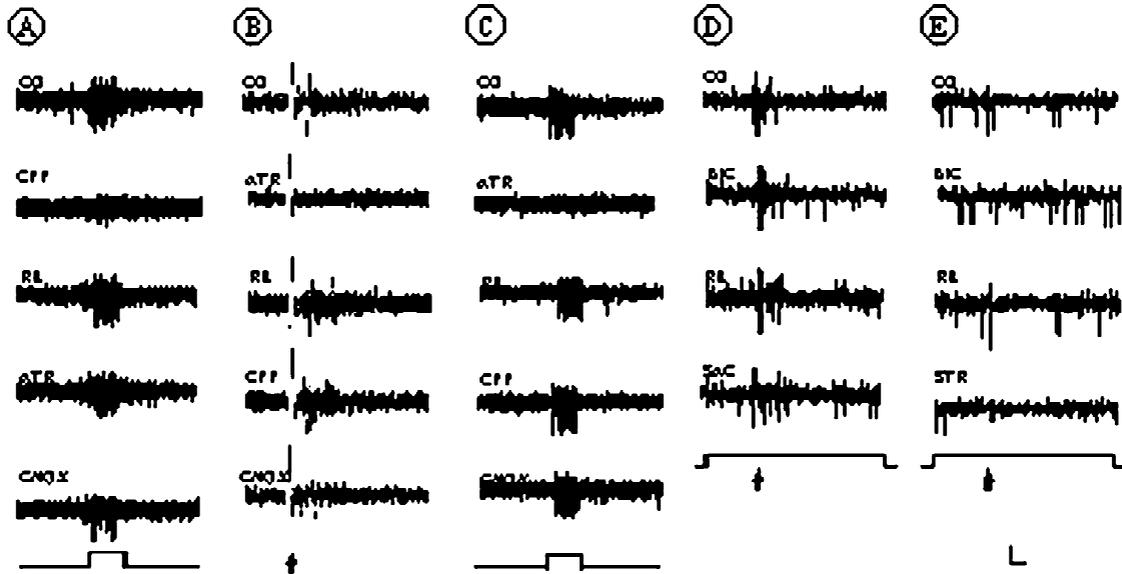


Fig. 4. Neuronal responses showing effects of glutamatergic (CPP, CNQX), cholinergic (ATR, atropine), GABAergic (BIC, bicuculline; SAC, 2-hydroxysaclofen), and glycinergic (STR, strychnine) antagonists on visual responses (A, C) and on responses evoked by electrical stimulation of the toad nucleus isthmi (B, D, E) in four tectal cells (responses in A and B were recorded from the same tectal cell). Visual responses in A were blocked by CPP but not by either atropine or CNQX, whereas those in cell C were selectively blocked by atropine, and by neither CPP nor CNQX. Excitatory responses of cell A–B to isthmic stimulations were selectively blocked by atropine, and not influenced by CPP and CNQX. Excitatory responses of E–I type cell D were selectively blocked by atropine (not shown), and its inhibitory responses were released by bicuculline but not by hydroxysaclofen. In I-type cell E, visual responses were inhibited by isthmic stimulations, and this inhibition was released by bicuculline but not affected by strychnine. Three sweeps were superimposed. Co, control; RE, recovery. Arrows point to electrical stimulus artifacts. Upward deflection of bottom traces represents visual stimulation using an 8° black disc. Scale bars: 20 mV, 500 ms in A and C, 10 ms in B, and 20 ms in D and E. From Ref. [126].

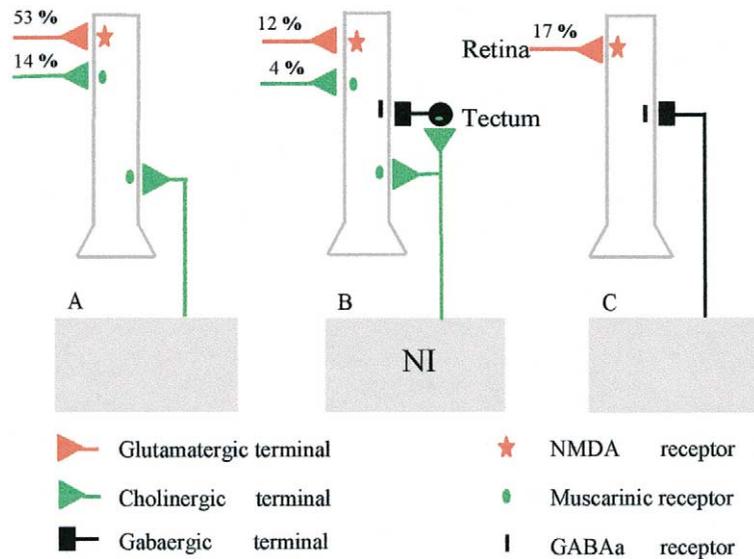


Fig. 5. Neuropharmacological experiments on toads have revealed convergence of retinal and isthmic afferents on tectal neurons in five combinations with respect to neurotransmitters and receptor subtypes utilized at the excitatory and inhibitory synapses. Tectal cells with cholinergic (green) isthmotectal synapses receive either glutamatergic (red) or cholinergic input from the retina (A), tectal cells receiving both cholinergic and indirect GABAergic (black) afferents make either glutamatergic or cholinergic synapses with retinal afferents (B), and tectal cells make both GABAergic synapses with isthmotectal terminals and glutamatergic synapses with retinotectal terminals (C). The percentage-numbers on the retinotectal terminals indicate proportion of each wiring mode in the total population of tectal neurons examined. Key symbols are listed in the lower part of the figure. Black solid circle represents the cell body of an interneuron.

2.2. Magnocellular and parvocellular divisions of avian NI differentially modulate tectal activity

The tecto-isthmic system in birds is a good model for studying the isthmic actions on tectal activity, because the isthmic complex in birds is considered to be composed of Imc, Ipc and Slu, and therefore the dual actions might be shared by these subdivisions separately. Although the electrophysiological properties of Imc and Ipc have been extensively studied, physiological knowledge on Slu is still lacking. Recently, our study provides the first electrophysiological evidence that the pigeon Slu is a visual center and its neurons are sensitive to motion, with some cells responding to motion in an inhibitory manner [129]. Therefore, our discussion below will focus on differential actions of Imc and Ipc on tectal activity as shown in three series of experiments. In the first series of experiments, microinjection of lidocaine, a local anesthetic that operates as a sodium-channel blocker, into Imc results in a significant reduction of the visual firing rate in most tectal cells, but lidocaine in Ipc does not affect the visual responses. The reason why lidocaine does not work in Ipc is elucidated below in the third series of experiments. In contrast, injection of NMDA into Ipc produces a significant decrease in the visual responses of tectal cells, but NMDA does not work in Imc due to the local absence of NMDA receptors [122]. These results imply that the Imc-tectal pathway is excitatory, whereas the Ipc-tectal pathway is inhibitory [106]. This conclusion is confirmed by the second series of experiments using microiontophoretic

techniques. Electrical stimulation of Imc induces spikes in tectal cells, showing the excitatory nature of the Imc-tectal pathway. This pathway is mediated by two different neurotransmitter systems, a cholinergic system that is blocked by atropine, and a glutamatergic system that is blocked by CPP or CNQX, an antagonist to AMPA receptors [107] (Fig. 6). On the other hand, electrical stimulation of Ipc produces inhibitory responses in 80% of tectal cells and a brief excitation followed by an inhibitory period in 20% of tectal cells examined. Both inhibitory mechanisms are blocked by bicuculline, an antagonist to GABA, but not by strychnine, an antagonist to glycine [15] (Fig. 7). It appears to contradict the previous finding that Ipc neurons can take up exogenous glycine [45], and that tectum releases pre-injected glycine during electrical stimulation of Ipc [74]. This discrepancy could be explained by suggesting that uptake affinity for and release of an exogenous chemical, for example glycine pre-injected into tectum, may be not a sufficient criterion for identifying a transmitter [44]. The brief excitatory responses preceding the inhibition during Ipc stimulation is blocked by atropine, showing its muscarinic and thus cholinergic nature [22]. Comparison of the dual actions of single NI on tectal cells in amphibians and the dichotomous actions of the isthmic complex in birds clearly shows that the excitatory and inhibitory actions of single NI are shared by Imc and Ipc, respectively (Fig. 8A). Furthermore, both excitatory and inhibitory actions of isthmic cells converge on the same tectal cell [109]. Although GABA-immunoreactive perikarya are found in the avian Imc [11,26,87],

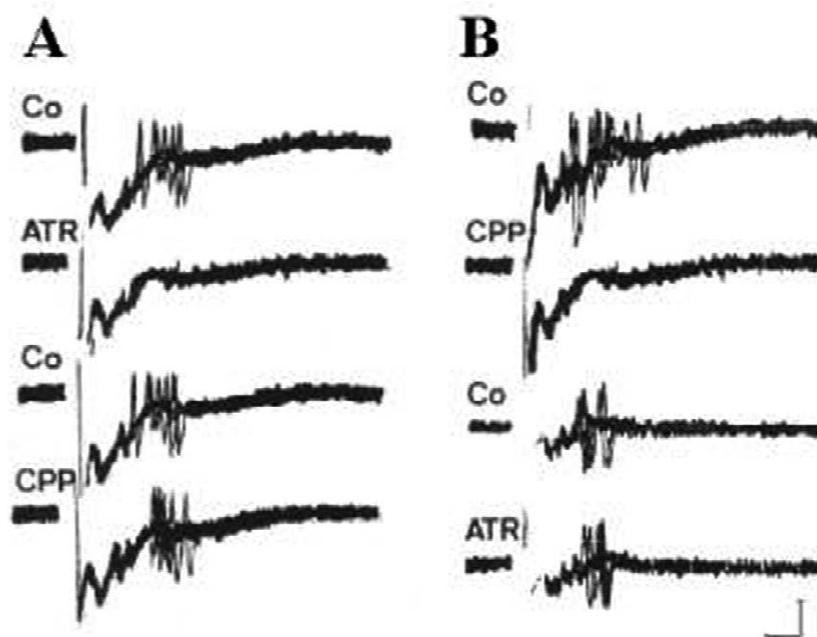


Fig. 6. Synaptic transmission from the nucleus isthmi pars magnocellularis (Imc) to optic tectum is mediated by acetylcholine (A) and glutamate (B). A: Effect of microiontophoretically applied atropine sulphate (ATR, 25 nA) and CPP (50 nA) on an acetylcholine-selective tectal cell following electrical stimulation of Imc. B: Effect of atropine sulphate (50 nA) and CPP (25 nA) on a glutamate-selective tectal cell following Imc stimulation. Six superimposed sweeps. Co, control. Scales: 1 ms, 0.5 mV/cm. From Ref. [107].

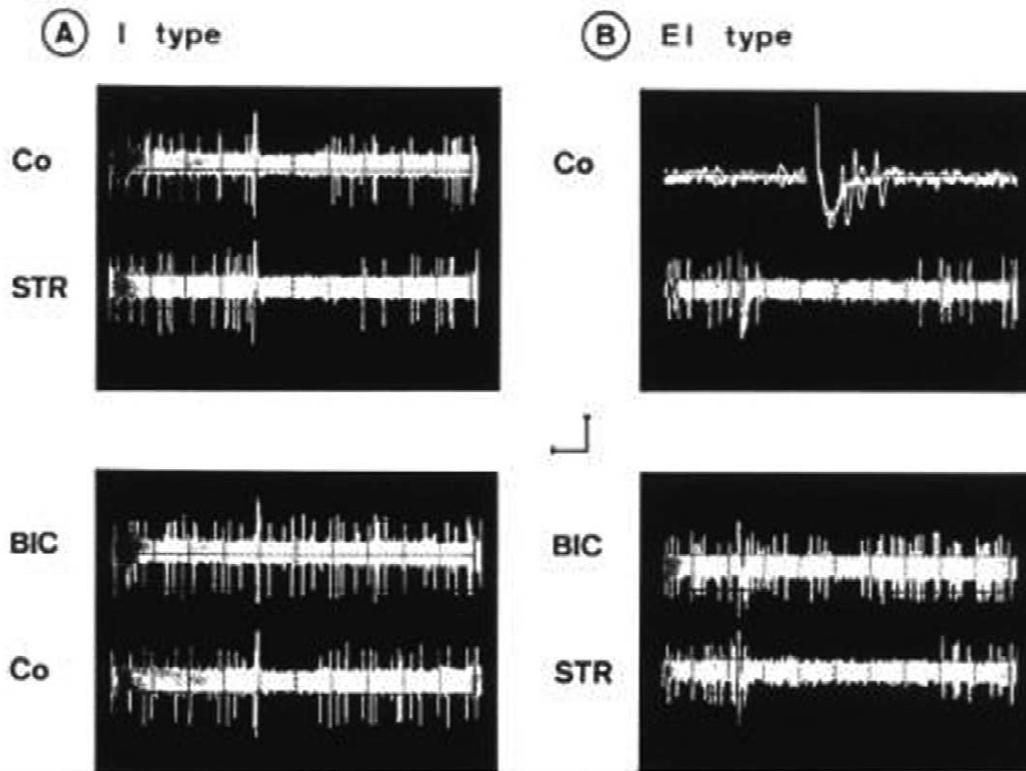


Fig. 7. Synaptic transmission from the nucleus isthmi pars parvocellularis (Ipc) to optic tectum is mainly mediated by gamma-aminobutyric acid (GABA). A: Inhibitory (I) type. Electrical stimulation of Ipc inhibits tectal cells, and inhibitory period is blocked by bicuculline (50 nA) but not by strychnine (50 nA). B: Excitatory-inhibitory (E-I) type. Electrical stimulation of Ipc evokes an excitation followed by an inhibition in tectal cells. Excitation is blocked by atropine but not by CPP (not shown) whereas inhibition is blocked by bicuculline (BIC, 50 nA) but not by strychnine (STR, 50 nA). Three superimposed sweeps. Scales: 0.5 mV/cm for all traces; 20 ms in A, 10 ms in B except upper trace as control (Co, 2 ms). From Ref. [15,22].

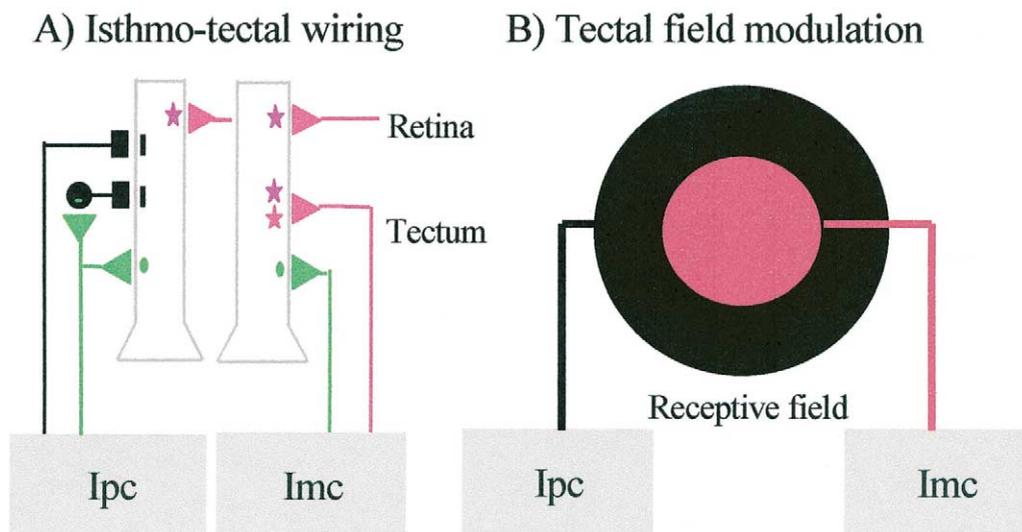


Fig. 8. Isthmo-tectal wiring (A) and dichotomous modulation of the receptive field of tectal neurons (B) in pigeons. The nucleus isthmi pars parvocellularis (Ipc) and the nucleus isthmi pars magnocellularis (Imc) exert inhibitory action through GABAergic (black) synapses and excitatory actions via glutamatergic (red) and cholinergic (green) synapses on tectal cells, respectively. A small proportion of Ipc-tectal fibers can produce in tectal cells a brief cholinergic excitation followed by an inhibitory period possibly via GABAergic interneurons. Although two tectal neurons are drawn in (A) for clarity, both Ipc-tectal and Imc-tectal afferents actually converge onto the same tectal cells. Chemical blockade and excitation of the isthmic complex show differential modulation of the excitatory and inhibitory regions of the receptive field of tectal neurons by Imc and Ipc, respectively. Key symbols in (A) are the same as in Fig. 5, with additional stars in purple representing AMPA receptors. Circle in red and ring in black (B) symbolize the excitatory and inhibitory receptive fields of a tectal cell, respectively.

they only occupy 40% of Imc cells in the pigeon [113], which are probably not Imc-tectal projection neurons. On the other hand, Imc cells are stained for ChAT and AChE [60,114], suggesting that they may use acetylcholine as one of transmitters. GABA-stained perikarya are found in the rostral Ipc, suggesting that some of Ipc neurons may be GABAergic [43–45,113]. Neurons in Ipc contain both AChE and ChAT and they are therefore cholinergic [60,114]. These cholinergic and possibly excitatory neurons of Ipc may exert inhibitory actions on tectal cells through the horizontally organized system of inhibition within the tectum [43,45]. In addition, retinotectal transmission in birds is glutamatergic [12,50,98] and mediated by AMPA receptors, although tectal cells could be excited by both AMPA and NMDA [12,50]. A small portion of retinal ganglion cells can monosynaptically inhibit tectal cells in frogs [61,62,105] and in pigeons [59]. They may use GABA as an inhibitory transmitter, but the functional significance of this retinotectal inhibition remains to be elucidated.

2.3. Excitatory and inhibitory receptive fields of tectal cells are modulated respectively by Imc and Ipc in birds

The third series of experiments on the isthmoc complex would demonstrate how Imc and Ipc could modulate the receptive field organization of tectal cells [109]. The receptive field of tectal cells in birds is usually composed of an excitatory (ERF) and an inhibitory receptive field (IRF) [20,48,34]. Its electrophysiological properties are closely related to those of the retinal ganglion cells and are modulated by input from extratectal sources such as the visual wulst and NI [1,17,53,99]. Microinjection of lidocaine into Ipc results in shrinkage or elimination of IRF, without significant influence on ERF. This change in the receptive field organization could explain why lidocaine injected into Ipc could not produce suppressive effects on visually driven activity of tectal cells in most cases, since only visual firing produced by motion within ERF was measured in those experiments [106]. Lidocaine injected into Imc, however, significantly reduced ERF in size, which was taken over by IRF. On the other hand, excitation of Ipc cells by NMDA resulted in an expanded IRF and a shrunk ERF, whereas excitation of Imc cells by acetylcholine lead to a decrease in IRF extent, without observable changes in ERF. In latter cases, the visual responses of tectal cells were significantly enhanced and inhibitory effects of IRF on ERF were markedly decreased. These data clearly show that the excitatory and inhibitory regions of the receptive field of tectal cells are strongly modulated by Imc and Ipc, respectively (Fig. 8B). This conclusion is firmly supported by the previous study showing that Imc and Ipc can differentially modulate the visual responses of tectal neurons in pigeons [106].

Hubel and Wiesel [41] proposed that the receptive field of a simple cortical cell is constructed from aligned

receptive fields of geniculate afferents presynaptic to the cell. This hypothesis is further supported by subsequent studies [6,16,55]. Furthermore, the receptive field of complex cells is also constructed with involvement of simple cells [65]. Both excitatory and inhibitory interactions within the cortex also play important roles in constructing cortical receptive fields [94]. Wang and Frost [110] found that receptive fields of Ipc and Imc cells in pigeons are very large and ovoid-shaped with elongation in vertical dimension, and thus supposed that they are formed by convergence of inputs from a group of tectal neurons in a vertical strip of tectum. This suggestion has received some anatomical evidence showing that the different scaling of tectal dimensions represented within Ipc would be likely to produce the vertically elongated receptive fields of isthmoc neurons [36]. Unlike simple or complex cortical cells [41], both Ipc and Imc cells respond to a moving bar within ERF without spatial summation and stop firing as long as the bar moves in IRF surrounding ERF [110]. Axons of Ipc and Imc cells give off broad branches in the tectum and make connections with tectal cells [85,87]. It is conceivable that an Ipc cell or an Imc cell with a large elongated receptive field could modulate the visual responsiveness of a group of tectal cells within a tectal column. This reciprocal and topographical relationship between tectal and isthmoc neurons ensure that small receptive fields of a group of tectal cells can be covered by a large receptive field of an isthmoc cell. This spatial overlap of receptive fields of both tectal and isthmoc neurons is a necessary condition for studying modulatory action of isthmoc cells on tectal cells [106,109]. Within the tectum, isthmotectal terminals may make axo-axonal synapses with retinotectal terminals presynaptic to tectal cells, or be interposed between retinotectal terminals and tectal dendrites, or share the same postsynaptic target with retinotectal terminals [117]. In the first two circumstances, isthmoc afferents could strongly control retinotectal transmission with gating mechanisms. This notion is supported by the finding that retinotectal transmission can be facilitated presynaptically by activity of the cholinergic projections from NI or from the parabigeminal nucleus [4,53,83], though few, if any, of cholinergic receptors are likely to be located on optic fiber terminals [5]. Electron microscopic observations on amphibians have indicated that isthmotectal terminals make synapses with dendrites of tectal cells in the superficial layers where retinal axons terminate [33]. In birds, paintbrush endings of Ipc axons terminate in the tectal layers where bottlebrush dendritic endings of tectal ganglion cells terminate, implying that Ipc-tectal projection might also play a role in motion detection [Luksch, Major and Karten, pers. comm.], possibly working together with tectal ganglion cells whose bottlebrush endings and large receptive fields are characteristics for detecting motion [63,89]. In the bushbaby, parabigeminal terminals are presynaptic to dendritic shafts of tectal cells that receive retinal afferents; thereby the cholinergic [67] parabigemi-

nal input might locally modulate retinal input on some tectal cells [13]. Electrical stimulation of the cat parabigeminal nucleus can excite tectal cells ipsilaterally [81]. Both retinal and parabigeminal terminals are also presynaptic to pale vesicle filled profiles, and therefore they could directly affect these presumed inhibitory elements in the superior colliculus [13]. It is likely that the parabigeminal nucleus also might exert dual actions on tectal cells in mammals.

3. Does the isthmo-tectal system work as a winner-take-all network?

These findings lend considerable support to the notion that the receptive field of visual neurons is a dynamic structure, sub-regions of which strongly interact with each other in the space-time domain [9,121]. The positive and negative feedback loops formed between the tectum and NI may work together in a winner-take-all network, so that the positive feedback loop could provide a powerful augmentation of activated loci, while the negative feedback loop may strongly suppress the others, thereby deciding who is the ‘winner’ [110]. For example, Imc could enhance the visual responses of tectal cells to target locations or stimulus features, while Ipc may suppress those to other locations or features in the visual field. Therefore, these processes could permit the animal to attend to only one of several competing visual targets simultaneously present in the visual field [29,78,106,110]. Some behavioral tests on amphibians with isthmic lesions seem to be consistent with this hypothesis. Frogs with isthmic lesions are unable to respond to a prey or threat visually presented in the visual field [32], and toads with lesions of bilateral NI can not select a single target when several targets are present in the visual field [8]. However, up to date, no direct proof for the function of the tecto-isthmic system as a winner-take-all network has been obtained due to technical difficulties with such experiments. Lesion methods usually have substantial limitations, including incomplete lesions of a given structure and/or unwanted damages to some other neural structures, and thus possibly complicate the explanation of lesion results. The present review indicates that the tecto-isthmic system in birds is an excellent model for studying tectal modulation, because Ipc and Imc can modulate tectal activity in opposite ways. It is also probably an appropriate model for electrophysiological tests on the winner-take-all mechanisms by using naturalistic (virtual) stimuli, extracellular recordings and chemical manipulation of Ipc and Imc with different chemicals in the future.

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