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We reviewed recent studies in our laboratory which have investigated the neural mechanisms underlying photic entrainment of the mammalian circadian system. The results from studies of extracellular single-unit recordings and of photic induction of Fos-like immunoreactivity (-lir) indicated that excitatory amino acid (EAA) transmission, and particularly, activation of the NMDA receptor subtype, is important for conveying photic information to suprachiasmatic nucleus (SCN) cells. We have also found that a sub-region of the SCN still shows Fos-lir after blockade of EAA receptors, and we have evidence suggesting that these cells are innervated by a distinct subdivision of the retinal projection to the SCN. In addition, we have found that photic responses of cells in the intergeniculate leaflet (which projects to the SCN) and of SCN cells are modulated by serotonin via a receptor that resembles the $5HT_{1A}$ subtype.

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NEUROPHYSIOLOGICAL ANALYSIS OF CIRCADIAN RHYTHM ENTRAINMENT

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ABSTRACT

We review recent studies in our laboratory which have investigated the neural mechanisms underlying photic entrainment of the mammalian circadian system. The results from studies of extracellular single-unit recordings and of photic induction of Fos-like immunoreactivity (-lir) indicate that excitatory amino acid (EAA) transmission, and particularly, activation of the NMDA receptor subtype, is important for conveying photic information to suprachiasmatic nucleus (SCN) cells. We have also found that a sub-region of the SCN still shows Fos-lir after blockade of EAA receptors, and we have evidence suggesting that these cells are innervated by a distinct subdivision of the retinal projection to the SCN. In addition, we have found that photic responses of cells in the intergeniculate leaflet (which projects to the SCN) and of SCN cells are modulated by serotonin via a receptor that resembles the $5HT_{1A}$ subtype.

The goal of our research program is to understand the physiological mechanisms underlying photic entrainment of the mammalian circadian system. Light information reaches the mammalian circadian pacemaker exclusively via the paired retinae and is conveyed through the optic nerves to two structures in the diencephalon: the suprachiasmatic nucleus (SCN) in the hypothalamus and the intergeniculate leaflet (IGL) in the thalamus (Moore, 1973; Harrington et al., 1985). Anatomical studies have demonstrated that the SCN is innervated at least in part by retinal ganglion cells that also project to the lateral geniculate nuclei (Millhouse, 1977; Pickard, 1985). Cells in the IGL and adjacent parts of the ventral lateral geniculate nuclei, in turn, project to the SCN, forming the geniculohypothalamic tract (GHT); some of the cells forming the GHT contain neuropeptide Y (NPY); others contain enkephalin, and there are probably also other unidentified transmitters (Card and Moore, 1989; Harrington et al., 1985; Morin et al., 1992). Cells in and near the SCN also project back to the IGL region of the geniculate (Morin et al., 1992), so these structures are richly interconnected via both direct and indirect routes.

One of our approaches to understanding the physiology of photic entrainment involves extracellular recordings of SCN and IGL cell firing rates in both *in vitro* slice preparations from hamsters and rats and in anesthetized intact animals. Another approach involves studying the photic regulation of SCN cell gene expression and its pharmacological basis.

EXCITATORY AMINO ACIDS

Neurophysiological studies of responses of SCN cells to light have indicated that SCN cells respond to diffuse retinal illumination sluggishly and often with sustained changes in firing rates (Groos and Mason, 1980; Meijer et al., 1986). Although sustained changes in firing-rates in response to sustained changes in illumination are characteristic of both SCN and IGL cells (as tested with durations of over 1 h for some IGL cells), they differ in their response latencies (Meijer et al., 1986; Harrington and Rusak, 1989). In one sample, SCN cells showed average latencies to respond to illumination of 61.4 ± 7.4 (SEM) ms (n=7), while IGL

cells showed latencies of 4.2 ± 0.8 ms (n=10) (S.-W. Ying, unpublished observations). SCN cells also show graded responses to increasing total luminance reaching the eyes, with responses beginning at high thresholds and saturating 2-3 log units above threshold (Meijer et al. 1986; Meijer and Rietveld, 1989). These cells, therefore, seem to function as luminance detectors, tracking intensity changes with firing rate changes, and maintaining these firing rates at stable levels over long intervals.

We have also recorded from SCN cells in slices maintained *in vitro* and have examined the effects of putative transmitters on firing rates to see if any of these mimic the known effects of light on SCN cells. A number of studies have suggested that an excitatory amino acid (EAA) is involved in mediating photic input via the direct retinohypothalamic tract (RHT) projection to the SCN, as appears also to be the case for other parts of the visual system (Shibata et al. 1986; Liou et al, 1986; Cahill and Menaker, 1989; Colwell et al., 1990; Kim and Dudek, 1991). We examined the effects of lengthy applications of EAA transmitters on SCN cells and found that glutamate activated most cells, as did kainate and quisqualate, which are agonists for the AMPA receptor, but for some cells responses declined during continuous application of these agonists. The selective agonist N-methyl-D-aspartate (NMDA) also activated SCN cells and did so in a sustained, dose-dependent fashion, which mimicked the sustained responses of SCN cells to photic input in the whole animal. Activation of SCN cells by NMDA could be attenuated by co-application of the selective, competitive NMDA antagonist APV, but it had little effect on kainate-induced activations (Mason and Rusak, 1991).

Electrical stimulation of the chiasm underlying the SCN in the slice preparation also activated SCN cells and this effect was also attenuated by APV treatment. This result suggests that sustained activation of the SCN via the optic nerves depends on an NMDA-regulated ion channel. This conclusion appears to contradict the conclusions from field potential studies (Cahill and Menaker, 1989) and intracellular studies (Kim and Dudek, 1991) of SCN responses to optic nerve stimulation. In the intracellular study, Kim and Dudek (1991) found that excitatory postsynaptic potentials in SCN cells evoked by optic nerve stimulation are

mediated primarily by non-NMDA mechanisms, with only a small, late component being sensitive to an NMDA antagonist.

In fact, there is no contradiction between these findings, since the intracellular and field potential studies monitored transient potentials evoked by single, very brief (0.15 or 0.5 ms) stimulations of the optic nerves. By contrast, we used continuous drug applications, electrical stimulation or photic input (in vivo) lasting from many seconds to several minutes in our studies, which probably more closely mimic the time course of entraining stimuli. The transient evoked potentials mediated by non-NMDA mechanisms probably function as a gating mechanism that allows continued photic input to act through slower, voltage-dependent NMDA channels to permit sustained changes in SCN cell firing rates. Similar conclusions have been reached for cells in the lateral geniculate nuclei (cf. Sillito et al., 1990). NMDA channels appear to play a role once neurons have been partially depolarized (Kim and Dudek, 1991), which could happen via the rapid activation of non-NMDA receptors. It is, however, the sustained activation of SCN cells through an NMDA channel that appears to be critical to the mediation of photic entrainment effects (cf. Colwell et al., 1990). This point is emphasized by *in vivo* recordings from SCN cells in rats, in which we have shown that local APV iontophoresis can block activation of SCN cells by NMDA and can also block activation of these cells by sustained retinal illumination (R. Mason and B. Rusak, in preparation).

The identity of the native RHT transmitter remains uncertain. The dipeptide N-acetyl-aspartyl-glutamate (NAAG) is found in retinal terminals in the SCN (Moffett et al, 1990) so we investigated its effects and that of its two metabolites, N-acetyl-aspartate (NAA) and glutamate. Glutamate, like NMDA, readily activates nearly all SCN cells, while NAA is ineffective. By contrast, the effects of NAAG applications are quite variable. On different SCN cells, NAAG had no effect, potentiated the effects of NMDA, or activated cells on its own (M. Mirmiran, personal communication, 1992; R. Mason, H.D. Piggins and B. Rusak, in preparation). The reason for this variability remains unclear. It may be that NAAG directly affects an EAA receptor or that it is rapidly metabolized to form glutamate, which affects

receptors. A NAAG-specific dipeptidase has been identified in other parts of the brain, including parts of the visual system (Slusher et al.,1992). If the dipeptidase were found in the SCN, NAAG could be metabolized there to form glutamate after it is released from RHT terminals. Whether the active agent is NAAG or glutamate, variable enzyme levels in different slices may produce quite different results. We intend to pursue the issue by attempting to correlate enzyme levels in SCN tissue with NAAG responsiveness.

Fos

To further examine the role of EAA receptors in transmission of photic information to the SCN, we also took advantage of our previous findings that nocturnal light pulses stimulate expression of *c-fos* and other genes in the hamster SCN (Rusak et al., 1990; see Kornhauser et al., 1993 for review). We first showed that peripheral administration of the non-competitive NMDA antagonist MK-801 (dizocilpine) can block photic induction of Fos immunoreactivity in most regions of the SCN (Abe et al., 1991). We then used both systemic administration of ketamine (a non-competitive NMDA antagonist) and intracranial injections of CPP and DNQX (selective, competitive NMDA and non-NMDA antagonists) and found very similar results: both NMDA and non-NMDA antagonists given before nocturnal light pulses suppress Fos expression in large portions of the SCN (Abe et al., 1992). A role for both types of ionotropic glutamate receptors in mediating light effects on Fos expression in SCN cells is consistent with the hypothesis that non-NMDA activation functions as a gating mechanism for sustained activation through the voltage-sensitive NMDA channel. Blockade of either channel could prevent NMDA receptor-mediated Ca^{2+} influx, which may be critical to activation of gene expression (Sheng and Greenberg, 1990).

Despite the efficacy of EAA antagonists in blocking Fos expression in most of the hamster SCN, the dorsolateral portion of the caudal SCN continues to respond to nocturnal retinal illumination with expression of Fos immunoreactivity (Abe et al., 1991; Ebling et al., 1991). It is unlikely that this region simply does not get a sufficient dose of antagonist, since

the drug doses used are large, and the region is not normally particularly heavily labeled compared to the rest of the SCN. Although immunocytochemical studies of transmitters in the SCN have not indicated that this region is neurochemically distinctive (Card and Moore, 1984: Morin et al., 1992), our results imply a transmitter/receptor system in this portion of the SCN which differs from that operating in the remainder of the SCN. This difference might reflect either a role for an EAA receptor which has not been blocked by the antagonists studied so far, or for a different class of receptor which we have not yet identified.

One possibility we considered is that these cells may be activated indirectly via photic activation of IGL cells which project using a non-EAA transmitter. Since we know that cells projecting from the IGL to the SCN are light responsive (Harrington and Rusak, 1989; Zhang and Rusak, 1989b), this hypothesis seems reasonable. We examined it by implanting stimulating electrodes into the lateral geniculate region and testing whether stimulation can activate Fos expression in the SCN. We found that stimulation there does activate SCN Fos expression, and Fos immunoreactivity appears only in the dorsolateral portion of the caudal SCN (Abe and Rusak, 1992). Although this result appears to confirm the hypothesis, it is not obvious why activation via the GHT should be restricted to this area, given that the GHT projects to all of the retinorecipient region of the hamster SCN (Harrington et al., 1985).

To further test the hypothesis that this activation represents IGL input to the SCN, we have recently made knife cuts around the SCN to prevent input from caudal regions (including the IGL) from reaching it, and in other animals we have made IGL/vLGN lesions, and then given MK-801 and a light pulse. With MK-801 blocking activation in most of the SCN and the lesions eliminating IGL input, we expected to see a complete lack of Fos in the SCN, yet Fos-lir still appeared in the dorsolateral SCN.

An alternative explanation is that IGL stimulation can antidromically activate retinal cells projecting to the IGL and that this activation is conveyed via the RHT back to a portion of the SCN, resulting in dorsolateral Fos expression. We now have preliminary results suggesting that ocular enucleations prevent the appearance of Fos-lir in the dorsolateral SCN after IGL

stimulations (H. Abe and B. Rusak, unpublished). Confirmation of these results would imply the existence of a class of retinal ganglion cells influencing the IGL and dorsolateral SCN using receptor mechanisms different from those operating in the rest of the SCN.

SEROTONIN

We have also begun a series of studies examining the role of serotonin (5-HT) in modulating photic responses of SCN and IGL cells, and the receptor subtypes involved. Serotonin and its interaction with light andthe circadian system are of interest for several reasons. First, there is a strong serotonergic projection from the raphe nuclei to both the SCN and the IGL (see Meijer and Rietveld, 1989; Mantyh and Kemp, 1983). Second, both serotonergic mechanisms and light are involved in some mood disorders (Skwerer et al., 1988), and, finally, serotonin can have a potent phase-shifting influence on the SCN in vitro and on behavioral rhythms (Edgar et al., 1993; Medanic and Gillette, 1992; Tominaga et al., 1992).

In our first study, we showed that microiontophoretic application of either 5-HT or the selective 5-HT_{1A} agonist 8-OH-DPAT to IGL cells in an anesthetized *in vivo* preparation suppresses spontaneous firing activity during darkness and reduces the responses of these cells to photic input (Zhang and Rusak, 1989a). We recently extended this study and showed that suppression of IGL cell firing rates by these 5-HT agonists is dose-dependent and not accompanied by changes in action potential waveforms. Co-application of the nonspecific serotonin antagonist metergoline was effective in antagonizing the effects of both 5-HT and 8-OH-DPAT. Furthermore, the selective 5-HT_{1A} antagonist, pindobind, when applied alone, does not alter cell firing rates significantly, but it can antagonize the effects of 8-OH-DPAT on IGL cell photic responses. These results suggest that 5-HT and 8-OH-DPAT act primarily through a receptor subtype resembling the 1A receptor. Other putative 5-HT_{1A} antagonists, pindolol, spiperone and propranolol, were either weak or ineffective in blocking the action of 8-OH-DPAT, although solubility problems might be limiting for pindolol in iontophoretic

experiments. Ketanserin, a 5-HT_2 antagonist and ritanserin, a 5-$HT_{2/1C}$ antagonist, failed to antagonize the effects of 5-HT on IGL cells (S.W. Ying, D.X. Zhang and B. Rusak, manuscript submitted).

In addition, we have found that the pineal hormone melatonin suppresses both spontaneous firing activity and photic responses of IGL cells in a dose-dependent manner. Although melatonin is structurally similar to serotonin, these effects have not been reversed by the 5-HT antagonists we have tested, suggesting mediation via a different receptor.

These results sugge. . a role for a 5-HT_1 receptor, similar to the $5HT_{1A}$ subtype, in mediating serotonergic effects on IGL cells, although other subtypes may contribute to the response. We are now examining the influence of 5-HT receptors on electrophysiological responses of hamster SCN cells to light, and we have preliminary evidence that 8-OH-DPAT is also effective in attenuating photic responses of these cells *in vivo* (S.W. Ying and B. Rusak, unpublished).

SUMMARY

Our results indicate a role for EAAs and both NMDA and non-NMDA types of receptors in mediating transmission of light information to the SCN. We have found evidence that NAAG can play a role, but the nature of that role and the conditions under which NAAG has its effects remain to be clarified. We have also shown that there is a retinal projection to parts of the SCN which does not involve an EAA (at least not one we have yet successfully antagonized), and tentative evidence that the retinal cells which project to this region also project to the IGL. We hope to identify these cells, their projections, and their transmitters. Finally, we have found that serotonin acting through a 5HT receptor which shares characteristics with the $5HT_{1A}$ receptor, and melatonin acting through a non-serotonergic mechanism, can alter photic responses of IGL and SCN cells. These results suggest mechanisms by which serotonin and melatonin can modulate photic entrainment of the mammalian circadian system. Our studies should help clarify the relations among the SCN, the

IGL and the raphe, and their contributions to the regulation of sleep, mood and circadian rhythms.

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