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The role of dopamine in the regulation of melatonin biosynthesis in vertebrate retina

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Abstract. The vertebrate retina rhythmically synthesizes melatonin, a hormone involved in the regulation of several intraocular processes cued by environmental lighting conditions. The rhythm of retinal melatonin production, with maximal synthesis at night in darkness, is driven by the photoperiodic environment to which animals are exposed, and is generated by an endogenous circadian clock(s). This article reviews data on the role of dopamine, an established retinal neurotransmitter and paracrine factor, as a mediator of acute suppressive and entrainment action of light on the melatonin generating system in the retina. Special emphasis is given to the characterization of dopamine receptor types involved in the control of retinal melatonin formation.

Key words: retina, melatonin biosynthesis, dopamine, dopamine receptors

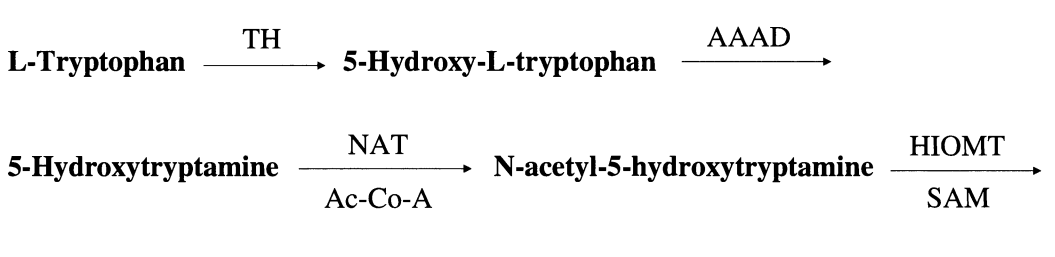
INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous putative neuromodulator in retinas of various vertebrate species (Besharse et al. 1988, Zawilska 1992, Zawilska and Nowak 1992). In contrast to the hormone of pineal origin, which exerts its actions at numerous target sites in the whole organism (Reiter 1984, 1991), melatonin produced by the retina is thought to act locally within the eye, and to play the role of a circadian signal and neurochemical analog of darkness and/or the "nighttime". Melatonin appears to be involved in the regulation of such rhythmic ocular events as adaptive photomechanic movements of photoreceptors and melanin granules in the retina-retinal pigment epithelium complex (Cheze and Ali 1976, Pang and Yew 1979, Pierce and Besharse 1985, Kemali et al. 1986), rod outer segment disc shedding and phagocytosis (Besharse and Dunis 1983), or sensitivity of second-order retinal neurons to light (Wiechmann et al. 1988). Furthermore, melatonin has been demonstrated to be a potent inhibitor of dopamine release and metabolism in the retina (Dubocovich 1983, Nowak 1988, Nowak et al. 1992).

Melatonin is synthesized from the amino acid precursor L-tryptophan by the consecutive actions of four enzymes: tryptophan hydroxylase (TH; EC 1.14.16.4), aromatic amino acid decarboxylase (AAAD; EC 4.1.1.28), serotonin N-acetyltransferase (NAT; EC 2.3.1.87) and hydroxyindole-O-methyltransferase (HIOMT; EC 2.1.1.4). The last two enzymes, i.e., NAT and HIOMT, require acetyl coenzyme A (Ac-Co-A) and S-adenosyl-L-methionine (SAM), respectively, as their cofactors.

As is the case for the pineal hormone, biosynthesis of the retinal melatonin follows distinct diurnal (or in some species circadian) variations, with high melatonin levels during the dark phase and low levels during the light phase of a natural or any imposed light-dark illumination cycle. This rhythmicity is clearly driven by the nocturnal stimulation of melatonin formation by an endogenous circadian oscillator(s). In fact, the rhythmic production of melatonin appears to be regulated primarily by distinct changes in the activity of NAT, which fluctuates in a manner similar to melatonin levels, with respect to both photoperiod and acute light exposure. Furthermore, an absolute amount of the synthesized melatonin is additionally dependent on serotonin availability during the whole period of high NAT activity. On the other hand, the activity of the last melatonin biosynthetic enzyme, i.e., HIOMT, does not seem to change as a function of photoperiod or lighting conditions (Nowak et al. 1989, Cahill et al. 1991, Thomas and Iuvone 1991, Zawilska 1992, Zawilska and Nowak 1992, Zawilska and Wawrocka 1993).

Our knowledge of the molecular mechanisms underlying the rhythmic melatonin production in the retina is still far from complete. Much of the work on the regulation of melatonin formation in the vertebrate retina has been guided by data obtained for the melatonin generating system in the pineal gland (Sugden 1989, Takahashi et al. 1989). It should be emphasized that both in the pineal gland and in the retina the regulatory mechanisms for melatonin content are directed at the level of the hormone synthesis. It is noteworthy and well documented that NAT is an inducible enzyme, and an increase of intracellular cAMP level seems to be an essential step in the induction and maintenance of high NAT activity (e.g. Morrisey and Lovenberg 1975, Deguchi 1979, Iuvone and Besharse 1983, Zawilska et al. 1992).



NEUROREGULATION OF MELATONIN BIOSYNTHESIS IN THE PINEAL GLAND: CRUCIAL ROLE OF NORADRENALINE

In rat pineal gland, the diurnal rhythm of melatonin production, as well as information about environmental lighting conditions, are imposed upon the gland by changes in the amount of neurotransmitter noradrenaline released into the perivascular space from sympathetic nerve terminals innervating the tissue. During the night (or the dark phase of an imposed light-dark illumination cycle) the electrical activity of these sympathetic nerves increases, and noradrenaline, which is released under these conditions, stimulates postsynaptic α- and β-adrenergic receptors. Stimulation of β-adrenergic receptors enhances adenylyl cyclase activity and elevates intrapinealocyte cAMP level. This increase in cAMP formation is markedly potentiated by concomitant stimulation of α_1-adrenergic receptors, which by itself has neglible effect on the cAMP-generating system (Sugden 1989).

In contrast, noradrenaline, through its interaction with postsynaptic α_2-adrenergic receptors (probably negatively linked to adenylyl cyclase) inhibits the dark-dependent rise in NAT activity and melatonin release from the pineal gland of chicken (Voisin and Collin 1986, Pratt and Takahashi 1987, 1988, Voisin et al. 1990). These experimental data set the stage for exploring a possible involvement of noradrenaline, and other catecholamines, in the regulation of melatonin biosynthesis in the vertebrate retina.

DOPAMINE IS A REGULATOR OF MELATONIN BIOSYNTHESIS IN VERTEBRATE RETINA

In their pioneering work performed on cultured eye cups of the African clawed frog, *Xenopus laevis*, Iuvone and Besharse (1986) demonstrated that dopamine, the predominant catecholamine in the vertebrate retina (Djamgoz and Wagner 1992), regulates retinal NAT activity. Although dopamine (10 μM) had no effect on NAT activity of *Xenopus* retina in light, it completely inhibited the nocturnal increase in the enzyme activity. The suppressive effect of dopamine on the dark-dependent increase in the retinal NAT activity was mimicked and blocked by dopamine receptor agonists and antagonists, respectively, but not by compounds acting at adrenergic receptors, an observation indicating an involvement of specific dopamine receptors. In line with the *in vitro* data, dopamine administered directly into the eye (intravitreally) also decreased the nighttime NAT activity of the chick retina in a dose-dependent manner, with an ED_{50} value of about 0.3 nmol/eye (Nowak and Zawilska 1994). Again, dopamine did not affect the enzyme activity in light-exposed retinas (Zawilska and Derbiszewska, unpublished data). The ability of benztropine, a dopamine reuptake inhibitor, and amphetamine, a dopamine-releasing agent, to inhibit the nocturnally-driven rise in NAT activity of the *Xenopus* and chicken retina (Iuvone and Besharse 1986, Zawilska and Iuvone 1989) strongly suggests that the endogenous dopamine acts similarly to the exogenously applied dopaminergic compounds, including dopamine itself.

As dopamine exerts its actions by stimulating specific receptors localized to membranes of target cells, further studies were conducted to elucidate the dopamine receptor subtype involved in the regulation of melatonin biosynthesis in the vertebrate retina.

D_4-LIKE DOPAMINE RECEPTOR MEDIATES THE INHIBITORY EFFECTS OF DOPAMINE ON MELATONIN BIOSYNTHESIS IN VERTEBRATE RETINA

In late 1980's, at the time when the first papers describing the pharmacological profile of the dopamine receptor regulating NAT activity and melatonin content of the retina were published (Iuvone 1986, Iuvone and Besharse 1986, Iuvone et al. 1987, Zawilska and Iuvone 1989), the classification

of dopamine receptors into D_1 type (positively coupled to adenylyl cyclase) and D_2 type (unlinked to stimulation of adenylyl cyclase) was widely accepted for various tissues (Kebabian and Calne 1979, Stoof and Kebabian 1984), including the retina (Schorderet and Nowak 1990). Based on this classification, dopamine receptors involved in the regulation of NAT activity in the retina of *Xenopus laevis* (Iuvone 1986) and chicken (Zawilska and Iuvone 1989, Nowak et al. 1990b) have been described as D_2 receptors. During the ensuing years, however, evidence from different experimental approaches suggested that the D_1/D_2 dopamine receptor classification was oversimplistic. Molecular biology techniques have led to the cloning, identification and characterization of novel dopamine receptor subtypes, termed D_3 and D_4 - members of the D2-family of dopamine receptors, and D_5 - a member of the D1-family of dopamine receptors (Sokoloff et al. 1990, Sunahara et al. 1991, Van Tol et al. 1991, Schwartz et al. 1992) in various tissues, including the retina (Cohen et al. 1992). Recently, in detailed pharmacological studies performed with an array of dopamine receptor agonists and antagonists, we re-evaluated the type of dopamine receptor regulating NAT activity in the chick retina. The role of the D_4-like dopamine receptor subtype (a close variant of a D_2 receptor) is strongly suggested by the following observations:

(1) The inhibitory effect of dopamine on nighttime NAT activity was significantly antagonized by blockers of the D2-family of dopamine receptors, spiroperidol and YM-09151-2 (emonapride), and clozapine (an atypical neuroleptic drug with high affinity towards D_4 subtype dopamine receptor; Van Tol et al. 1991), and was not affected by an antagonist of the D1-family of dopamine receptors, i.e., SCH 23390 (Zawilska and Nowak 1994a).

(2) The suppressive effect of dopamine on nighttime NAT activity in the chick retina was mimicked by agonists of the D2-family of dopamine receptors (given both intraperitoneally and intravitreally) with the following order of potency: quinpirole (a predominant agonist of D_3/D_4 receptors) > apomorphine = pergolide > (±)ADTN > 7-OH-DPAT (a selective D_3 receptor agonist) = bromocriptine (a predominant agonist of D_2/D_3 receptors). SKF 38393, an agonist of the D1-family of dopamine receptors, was inactive (Nowak and Zawilska 1994, Zawilska and Nowak 1993, 1994a).

(3) The suppressive effect of quinpirole on nocturnal NAT activity in the chick retina was antagonized, in a dose-dependent manner, by several blockers of the D2-family of dopamine receptors (injected intraperitoneally or intravitreally), i.e., sulpiride, spiroperidol, clozapine, and YM-09151-2. Interestingly, although sulpiride appeared to be a potent drug, there was no marked stereospecificity in its action, the observation suggesting an interaction of sulpiride with the D_4 dopamine receptor subtype rather than with the D_2 type (Seeman and Van Tol 1993). Raclopride, an antagonist of D_2/D_3 dopamine receptors, and remoxipride, a selective D_2 dopamine receptor antagonist, two drugs with very low affinity for the D_4 receptor (Van Tol et al. 1991, Lahti et al. 1993), did not modify the action of quinpirole (Zawilska and Nowak 1993, 1994a).

It is interesting to note that the dopamine receptor regulating NAT activity in the duck retina also appears to represent a D_4-like subtype (Zawilska and Derbiszewska, unpublished data). Since apomorphine, an agonist of the D2-family of dopamine receptors, has been demonstrated to decrease nighttime NAT activity in the rat and rabbit retina in a spiroperidol-sensitive manner (Nowak et al. 1989), the question still remains open as to whether this phenomenon also is mediated *via* stimulation of the D_4 dopamine receptor subtype.

In agreement with the postulated by us involvement of the D_4-like subtype dopamine receptor in regulation of retinal melatonin biosynthesis is a recent demonstration by Cohen et al. (1992) of D_4 mRNA in mouse retina, including photoreceptors - a primary site of melatonin biosynthesis in the retina (e.g., Wiechmann and Hollyfield 1989, Iuvone et al. 1990, Cahill and Besharse 1993). On the other hand, D_3 receptor mRNA probes yielded no label-

ling in mouse retina (Cohen et al. 1992), suggesting the absence of this subtype of dopamine receptor in the studied tissue. D_2 mRNA has been found in the outer nuclear layer of the human retina (Dearry et al. 1991), but it was not detected in photoreceptors of mouse (Cohen et al. 1992), monkey or rat retina (Stormann et al. 1990).

Intracellular cAMP is an important stimulatory factor involved in the complex process of NAT induction (e.g. Deguchi 1979, Iuvone and Besharse 1983, Iuvone et al. 1990, Zawilska et al. 1992, Nowak and Zawilska 1994). Activation of the retinal D_2-dopamine receptor has been found to decrease cAMP accumulation (Iuvone 1986, Qu et al. 1989, Nowak et al. 1990a,b). On the other hand, although the second messenger system(s) linked to the D_4-dopamine receptor has not been precisely characterized thus far, there are some indications that at least in the retina of mouse (Cohen et al. 1992) and chick (Derbiszewska and Zawilska, unpublished data) stimulation of this receptor subtype may decrease the intracellular cAMP level. Keeping this in mind, it seems likely that activation of D_2 and/or D_4 dopamine receptors, localized on the NAT containing cells, results in the suppression of the nocturnally- or pharmacologically-driven increase of NAT activity (and consequent melatonin formation) by a mechanism that in all likelihood involves receptor-mediated inhibition of adenylyl cyclase. This hypothesis is supported by our observation that in the chick and adult hen retina quinpirole suppressed (in a spiroperidol- and clozapine-sensitive manner) the enhancement of both NAT activity and cAMP production evoked by forskolin (a direct activator of adenylyl cyclase) and 3-isobutyl-1-methylxanthine (IBMX; an inhibitor of cyclic nucleotide phosphodiesterase). It did not modify the action of dibutyryl-cAMP (a non-hydrolyzable analog of cAMP)(Nowak et al. 1990b, Zawilska et al. 1991, Zawilska and Nowak 1994a, Derbiszewska and Zawilska, unpublished data). Similarly, in experiments performed on cultured eye cups of *Xenopus laevis*, and on photoreceptor-enriched monolayer cultured cells of chick embryo retina, dopamine potently inhibited forskolin- and IBMX-evoked increase of NAT activity. However, it had no effect on rises in the enzyme activity produced by non-hydrolyzable analogs of cAMP, which directly activate cAMP-dependent protein kinase (Iuvone, 1986, Iuvone and Besharse 1986, Iuvone et al. 1990).

DOPAMINE IS INVOLVED IN ACUTE INHIBITORY, BUT PROBABLY NOT IN PHASE-SHIFTING, ACTION OF LIGHT ON MELATONIN BIOSYNTHESIS IN VERTEBRATE RETINA

The observations that (1) dopamine mimics the acute inhibitory effect of light on NAT activity of the vertebrate retina (Iuvone 1986, Iuvone and Besharse 1986, Nowak and Zawilska 1994), and (2) light increases synthesis, release and metabolism of retinal dopamine (e.g., Iuvone et al. 1979, Parkinson and Rando 1983a,b, Godley and Wurtman 1988, Nowak 1988, Boatright et al. 1989), have led to the hypothesis that retinal dopamine may be a part of the pathways for light inputs to the melatonin system and/or the circadian oscillator. Light is a crucial environmental factor regulating melatonin biosynthesis in the vertebrate retina, and as such it has two distinct effects on the hormone production. Thus, light causes an acute suppression of NAT activity and melatonin content and release (e.g., Binkley et al. 1979, Iuvone and Besharse 1983, Hamm et al. 1983, Cahill and Besharse 1991, Zawilska et al. 1994), and it resets the phase of the free-running circadian oscillator generating the rhythm of NAT activity (Cahill and Besharse 1991, 1993, Zawilska 1994a).

Several antagonists of the D2-family of dopamine receptors, i.e., clozapine, spiroperidol, sulpiride, YM-09151-2 and haloperidol, given directly into the eye of light-adapted chicks markedly elevated the retinal NAT activity and melatonin content (Zawilska and Nowak 1994b). In harmony with this, intraocular pretreatment of birds with these drugs significantly attenuated the decline of night-

time NAT activity and melatonin content produced by a 30-minute exposure of the animals to light (Zawilska et al. 1994). In contrast, SCH 23390 (the antagonist of the D1-family of dopamine receptors), raclopride and remoxipride (two neuroleptics with very low affinity towards the D_4-dopamine receptor subtype) were ineffective (Zawilska and Nowak 1994b, Zawilska et al. 1994). Blockers of the D2-family, but not of the D1-family of dopamine receptors also antagonized the inhibitory effect of light on the nocturnal increase of NAT activity in the retina of *Xenopus laevis* (Iuvone et al. 1987) and adult hen (Nowak and Żurawska 1989). However, in these studies the effects of the drugs tested required the presence of cyclic nucleotide phosphodiesterase inhibitors. In the retina of chick and *Xenopus laevis,* blockers of dopamine receptors did not affect tissue nighttime NAT activity, which suggests that the retinal dopamine receptors inhibiting melatonin biosynthesis are occupied by the endogenous ligand in the light-adapted tissue (Iuvone et al. 1987, Zawilska and Nowak 1994b, Zawilska et al. 1994).

Light not only acutely suppresses melatonin synthesis in the vertebrate retina, but it also resets the phase of a free-running circadian oscillator generating the rhythm of the hormone production and release. Studies performed on superfused *Xenopus laevis* eyecups and cultured photoreceptors of *Xenopus* retina have demonstrated that pulses of white light caused phase-dependent phase-shifts seen in subsequent cycles of the circadian rhythm of melatonin release (Cahill and Besharse 1991, 1993). Light pulses produced phase delays when applied during the early subjective night, phase advances when applied during the late subjective night, and had no effect when presented during the subjective day. In accordance with the frog data, exposure of chicks to light during the subjective night resets the phase of the circadian rhythm of the retinal NAT activity *in vivo* in a phase-dependent manner (Zawilska 1994a). In subsequent studies on molecular mechanisms controlling the function of the circadian pacemaker system in the vertebrate retina, the effects of light and dopaminergic drugs on the rhythm of NAT activity (chick, *in vivo*) and melatonin release (*Xenopus, in vitro*) were compared. Activation of presumptive D_2 dopamine receptors in *Xenopus* retina, produced by dopamine and quinpirole, not only suppressed melatonin levels, but also affected the timing of the circadian rhythmicity of melatonin release in a manner similar to that of light (Cahill and Besharse 1991, 1993). Interestingly, although eticlopride (a D_2-dopamine receptor antagonist) blocked the phase delay of the circadian rhythm of melatonin release that was induced by dopamine, it had no effect on light-evoked circadian phase shifts (Cahill and Besharse 1991). These data provide evidence for the existence of a dopaminergic input to the ocular circadian clock localized in *Xenopus* retinal photoreceptors. However, they do not support the idea that light affects the circadian oscillator by acting exlusively *via* the dopaminergic pathway.

When quinpirole was administered to chicks at the beginning or in the middle of the subjective night, it produced a substantial and long-lasting decline in retinal NAT activity, but, interestingly, no sustained effects on the phase of the circadian oscillation in the enzyme activity were detected (Zawilska 1994a). Similar observations have been reported for the chick pineal gland, where light-induced acute suppression of melatonin biosynthesis was easily mimicked by noradrenaline and clonidine (acting at α_2-adrenergic receptors), whereas these drugs did not reset the phase of the pineal circadian oscillation (Zatz and Mullen 1988, Zawilska 1994b).

Based on the currently available data it seems reasonable to assume that in the chick retina dopamine is not involved in the complex process of entrainment of the circadian clock(s) controlling melatonin rhythmicity by light cycles.

PLASTICITY OF DOPAMINE RECEPTORS REGULATING MELATONIN BIOSYNTHESIS IN VERTEBRATE RETINA

There are some indications that dopamine receptors regulating melatonin biosynthesis in the retina

undergo adaptive changes in response to alterations in the intensity of the retinal dopaminergic neurotransmission. Injection of the neurotoxin kainic acid into the vitreous body of young chicks produced a dramatic decline in retinal levels of dopamine and its main metabolite - 3,4-dihydroxyphenylacetic acid (DOPAC), with a concomitant increase in sensitivity of dopamine receptors regulating tissue NAT activity (Zawilska and Iuvone 1992). On the other hand, prolonged (for 4 days) adaptation of chicks to constant darkness significantly decreased the retinal content of dopamine and DOPAC, reduced the dopamine/DOPAC ratio, and potentiated the suppressive effect of quinpirole (the predominant agonist of D_4-dopamine receptors) on NAT activity in chick retina (Zawilska 1992). Furthermore, following long-term (three weeks, once daily) administration of neuroleptic drugs, such as sulpiride and clozapine, both blockers of the D2-family of dopamine receptors, a hyperactivity of D_4-like dopamine receptors regulating NAT activity in the chick retina was detected (Zawilska, unpublished data). This observation raises a possibility that in patients chronically receiving drugs which increase or decrease central dopaminergic neurotransmission (e.g. patients suffering from schizophrenia or Parkinson's disease) adaptive changes in retinal melatonin production may develop. The problem of the extent to which such changes could affect physiological (and/or pathological) processes occurring within the eye awaits elucidation.

CONCLUDING REMARKS

Light is the most important environmental factor regulating melatonin biosynthesis in the vertebrate retina. Light has two effects on the melatonin-generating system: (1) to acutely suppress melatonin formation, and (2) to entrain and phase shift the rhythm of the hormone's synthesis. There is fairly good evidence that dopamine, released in response to light stimulation and acting on postsynaptic D_4-like (and/or D_2) dopamine receptors, is partially responsible for the light-induced suppression of retinal melatonin production. On the other hand, it is less clear whether the dopaminergic system is of major importance in the light-evoked process of entrainment of the circadian oscillator generating the rhythm of NAT activity, melatonin synthesis and release. Furthermore, the molecular mechanism(s) underlying dopamine receptor-induced suppression of NAT activity in the retina is not fully understood, although a possible involvement of the receptor-mediated inhibition of adenylyl cyclase activity has been suggested. Another unsolved question is the physiological (and pathological) significance of adaptive changes in the reactivity of dopamine receptors regulating melatonin biosynthesis in the retina of vertebrates, including humans. Finally, in light of a growing need for a simple animal model system with which to study D_4 dopamine receptor antagonistic properties of neuroleptic drugs, we propose the dopamine/quipirole evoked suppression of nocturnal NAT activity in the chick retina as a promising possibility.

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