Diurnal Pineal 3-O-Sulphotransferase 2 Expression Controlled by β-Adrenergic Repression*

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The 3-O-sulfotransferases (3OSTs) catalyze the addition of sulfate groups at the 3-OH site of glucosamine in heparan sulfate proteoglycans, which serve as critical mediators of various biological functions. We demonstrate that the 3OST2 isoform is expressed at high levels in the rat pineal specifically during the daylight hours. The dramatic diurnal rhythm of 3OST2 is regulated by central clock-controlled activities of the superior cervical ganglion, persists in constant darkness, and is inducible by light at nighttime. Importantly, 3OST2 transcription is blocked by β-adrenergic agonists that activate the pineal melatonin formation and is induced by β-adrenergic antagonists, which block melatonin production in vivo. Because of the inverse expression and regulation patterns of 3OST2 with serotonin N-acetyltransferase, the enzyme controlling the melatonin rhythm in the pineal, we tested the effects of forced expression of 3OST2 in the night pineals on N-acetyltransferase gene expression and melatonin production and found that, surprisingly, 3OST2 expression at night fails to interfere with melatonin synthesis. These data suggest 3OST2 may serve a unique function in the pineal that may be independent of melatonin formation.

Heparan sulfate proteoglycans are implicated as co-receptors in various processes including adhesion, proliferation, differentiation, and morphogenesis (1–3). The 3-O-sulfotransferases (3OSTs)3 perform the last enzymatic modification of a large number of steps required to generate a broad array of mature heparan sulfate proteoglycans that have distinct biological activities (4, 5). Four 3OST isoforms have been identified (6), three of which are shown to transfer sulfate to distinct disaccharides (7). For instance, the conversion of non-anticoagulant heparan sulfate to anticoagulant heparan sulfate requires 3OST1 (6, 7), which sulfates N-sulfated glucosamine groups (5).

On the other hand, 3OST3 is responsible for generating sites for the binding and initiation of herpes simplex virus type 1 entry (8).

The pineal gland is a midline neuroendocrine structure of the brain that synthesizes and secretes melatonin specifically at night to inform the body about environmental light and dark information (9). This rhythmic production of melatonin is dependent on the suprachiasmatic nucleus clock, which relays information to the pineal via the superior cervical ganglion (SCG) in the form of circadian norepinephrine secretion at night. Light dramatically reduces hormone output at night (9, 10).

To understand the molecular mechanisms underlying the dramatic oscillation and tight regulation of diurnal melatonin formation, we performed differential analysis of pineal day and night RNAs using subtractive hybridization (11) and identified a number of night- and day-specific transcripts. Previously we reported three of the night-specific molecules, namely serotonin N-acetyltransferase (NAT) (12), which is a crucial enzyme in melatonin synthesis, pineal night-specific ATPase (13) (PINA), an alternatively spliced product of Wilson disease gene ATP7B, and Patched 1 (14), which is a receptor for hedgehog signaling. One of the common features of these genes is that their transcriptions are all up-regulated by β-adrenergic signaling and suppressed by light, which terminates adrenergic inputs to the pineal.

In this paper we report the cloning and characterization of a day-specific 3OST2 expression in the pineal gland. Northern blot analysis reveals a dramatic diurnal rhythm of 3OST2 expression that persists in constant darkness and is abolished in constant light. We show that the rhythm is dependent on the superior cervical ganglion via adrenergic inputs to the pineal and is absent during early postnatal development. The night expression of 3OST2 is inducible by light, whereas the day expression is suppressed by β-adrenergic signaling that activates melatonin formation. Finally we demonstrate that forced night expression of 3OST2 does not prevent NAT gene expression nor does it affect melatonin secretion and its suppression by light in vivo.

EXPERIMENTAL PROCEDURES

Animals—All animal protocols were conducted in accordance with the institutional animal care and use committee. Adult male Sprague-Dawley rats purchased from Harlan Sprague-Dawley were housed in a temperature-controlled room under 14:10 light/dark conditions with lights-off at 1 a.m. for more than 1 week before experiments.

Cloning of Rat 3OST2 and Northern Blot Analysis—The subtractive hybridization of pineal day and night mRNAs has been previously described (Borjigin et al. (12)). Individual clones in the pineal day-specific subtracted cDNA library were used for PCR Southern and subsequently Northern blot analysis (11). The clone PL22 was specifically expressed during the daytime. GenBank™ analysis of PL22 re-
The expression of 3OST2 in the pineal gland displays marked circadian rhythm that is developmentally regulated. A, tissue distribution of 3OST2 gene expression. Each lane is loaded with 5 μg of total rat tissue RNA, except for the last two lanes, which were loaded with 10 μg of pineal day or night RNAs. The blot was first hybridized with a full-length 3OST2 probe, which was subsequently hybridized with GAPDH probe. B, temporal expression profiles of 3OST2 in the pineal. Five μg of pineal total RNA taken at the indicated times were loaded in each lane. Identical blots were hybridized with 3OST2 (upper panel), NAT (middle panel), and GAPDH (lower panel). C, 3OST2 expression is developmentally regulated. Day (2–4 p.m., D) and night (7–8 a.m., N) pineal RNA was taken from animals at birth (P0), on postnatal days 2 (P2), 5 (P5), 10 (P10), 20 (P20), and 30 (P30). Identical blots were hybridized with 3OST2 and GAPDH.

Fig. 1. 3OST2 expression in the pineal displays marked circadian rhythm that is developmentally regulated. A, tissue distribution of 3OST2 gene expression. Each lane is loaded with 5 μg of total rat tissue RNA, except for the last two lanes, which were loaded with 10 μg of pineal day or night RNAs. The blot was first hybridized with a full-length 3OST2 probe, which was subsequently hybridized with GAPDH probe. B, temporal expression profiles of 3OST2 in the pineal. Five μg of pineal total RNA taken at the indicated times were loaded in each lane. Identical blots were hybridized with 3OST2 (upper panel), NAT (middle panel), and GAPDH (lower panel) probes. C, 3OST2 expression is developmentally regulated. Day (2–4 p.m., D) and night (7–8 a.m., N) pineal RNA was taken from animals at birth (P0), on postnatal days 2 (P2), 5 (P5), 10 (P10), 20 (P20), and 30 (P30). Identical blots were hybridized with 3OST2 and GAPDH.

SCG Removal—A group of rats were sympathectomized by removal of both left and right SCG by surgical approach from between the sternohyoideus omohyoid muscles.

Surgery—Animals were deeply anesthetized with a combination of ketamine (10 mg/ml, 0.5 ml/100-g weight, intraperitoneal) and xylazine (2 mg/ml, 0.5 ml/100-g weight, intraperitoneal). The shaved head was positioned in a stereotaxic frame, and a 2-cm midline incision was made 10 mm posterior to the transverse suture extending to the occipital ridge. A circular opening (6.8 mm in diameter), centered midline 1.5 mm posterior to the confluence of the superior sagittal and transverse sinuses, was created using a dental burr drill equipped with a shank diamond wheel point (Dremel). The dura was exposed after grinding away the top bone and was removed by first making a cross-cut with a scalpel blade and then peeling away with fine forceps. The pin matter that covers the surface of the pineal was then removed carefully to visualize the pineal, which is connected to the confluence of the sinuses via the pineal vein. Three stainless steel screws were placed surrounding the opening on the skull to serve as anchors. The tip of the guide cannula (CMA/microdialysis) was then positioned immediately over the exposed pineal before closing the skull opening with dental cement. The guide cannula with the stylet was mounted on the skull with dental cement. After surgery, animals were housed in individual cages in light-controlled rooms described above and were allowed to recover for 24 h.

Microdialysis—Pineal microdialysis was carried out as follows. Immediately before sampling, the rat was anesthetized with halothane briefly, the stylet (or dummy probe) was replaced with a microdialysis probe (CMA12, 20-kDa cut-off, 3- or 4-mm length) (CMA/microdialysis) and fixed with plastic glue. The dialysis probe was continuously perfused via microbore PEEK tubing (inner diameter, 0.12 mm; outer diameter, 0.65 mm) at a flow rate of 2 μl/min with artificial cerebral spinal fluid (Harvard) that was pumped by a CMA/102 microdialysis pump. Blots were hybridized with the probes indicated. D, 3OST2 night expression was restored by removal of SCG. Bilateral superior cervical ganglia (SCGX) of adult rats were removed, and pineal RNAs isolated at 3 p.m. (D) or 7 a.m. (N) were analyzed with indicated probes after blotting.

Fig. 2. 3OST2 rhythm is controlled by a clock, light, and superior cervical ganglion innervation. A, diurnal rhythm of 3OST2 expression persists in constant darkness. Rats were placed in constant darkness for 48 h before tissue harvesting. Five μg of total pineal RNA taken from animals sacrificed at the indicated times were loaded in each lane. Identical blots were hybridized with 3OST2 and GAPDH. B, constant light elevates 3OST2 gene expression during the subjective night. Rats were placed in constant light conditions for 48 h before RNA was collected. Each lane was loaded with 5 μg of total pineal RNA. The sample collected at 3 a.m. was lost during the RNA preparation. Blots were hybridized with the probes indicated. C, light stimulates 3OST2 transcription. Rats were stimulated with light for hours indicated before harvesting of pineal RNA at 9 a.m. Three identical blots were hybridized with probes indicated. D, 3OST2 night expression was restored by removal of SCG. Bilateral superior cervical ganglia (SCGX) of adult rats were removed, and pineal RNAs isolated at 3 p.m. (D) or 7 a.m. (N) were analyzed with indicated probes after blotting.
pump. Samples were collected every 10 min via the PEEK tube into the 20-μl loop of an automatic injector (BAS, West Lafayette, IN), which is on-line with the HPLC system. The sample loop was set to be retained in the load (or collect) position during the 10 min and was automatically switched to the injection position very briefly, after which the cycle was repeated. The rats were linked to the apparatus for dialysis through a quartz dual channel swivel (Harvard) to prevent the tubing from entanglement.

HPLC—The analytical conditions for the detection of melatonin are based on Drijfhout et al. (15) with some minor modifications. A Shimadzu (Columbia, MD) pump was used in conjunction with Shimadzu fluorescence detector (excitation, 380 nm; emission, 345 nm). Samples were injected into the system through a Valco injection valve with BAS pollen 8 controller and subsequently separated on a reversed phase C18 column (250 × 4.6 mm, Supelco) set at a constant temperature of 30 °C using Shimadzu column heater controlled by the Shimadzu system controller. The mobile phase consisted of a mixture of 10 mM sodium acetate adjusted to a pH of 4.5 with concentrated acetic acid, 0.01 mM Na2-EDTA, 500 mg/liter heptane-sulfonic acid, and 20% (v/v) acetonitrile. The flow rate of the HPLC pump was set at 2 ml/min throughout the experiment. The chromatogram was set to run for 9 min, with the remaining 1 min for the system to be ready for the next trigger signal, which was provided by the BAS autoinjector controller. Standard solutions were used to calibrate the system. The automated control of the HPLC system and the programming of the flow rate as well as handling and storage of the chromatograms was done with an external computer with the Shimadzu Class-vp 5.03 chromatography software.

In Situ Hybridization Analysis—3OST2 (clone PL22.7, 3′-untranslated region of rat 3OST2), rat NAT, and rat tryptophan hydroxylase (the rate-limiting enzyme of serotonin synthesis) full-length cDNA probes were used for in situ studies as previously described (13). At the end of the microdialysis analysis of individual rats, rats were taken off the microdialysis devices and rapidly sacrificed. When the pineals were placed in Tissue-Tek (Sakura) compound for later sectioning, care was taken to keep the microdialysis membranes in the pineal for ease of orientation.

Adenoviral Vector-mediated 3OST2 Expression in Living Pineals—Recombinant adenovirus expressing full-length rat 3OST2 was generated by using the AdEasy system (16). The shuttle plasmid pAdTrack-CMV-3OST2 was transfected into HEK 293 cells with AdEasy-1 vector using LipofectAMINE (Invitrogen). The recombinant adenovirus Ad-CMV-3OST2:GFP, generated by homologous recombination in human embryonic kidney cells, was isolated, amplified, and titrated as described (16).

The surgical procedures used for exposing the pineals before injection of recombinant adenovirus were identical to those used for microdialysis probe implantation (see above). Immediately after the pineals were exposed, AdCMV-3OST2:GFP virus was injected into the pineal using a thin pulled glass pipette and nanojector II (Drummond Scientific Co.) through the microdialysis probes for 4 h (2 p.m. to 6 p.m.). Rats were taken off the microdialysis apparatus immediately after the microdialysis, and pineals were isolated immediately, serially sectioned, and analyzed using probes indicated. D, 3OST2 expression is activated by a β-adrenergic blocker. Melatonin secretion was monitored in individual rats for three cycles. Cycles 2 (solid circles) and 3 (open circles) are shown (upper panel). During the last circadian cycle, the pineals were infused with propranolol (PROP) for 8 h from 11 p.m. Rats were sacrificed at 7 a.m. (arrow), and pineals sectioned and analyzed for 3OST2, NAT, and TPH gene expression (lower panels).

**RESULTS**

3OST2 Is Diurnally Expressed in the Pineal—In a first round of screening of the subtracted day-specific pineal cDNA library, we found that 3OST2 expression is day-specific with no expression during the late night. Tissue distribution studies suggest that 3OST2 expression is the highest in the day pineal than in any other tissues examined (Fig. 1A), and no diurnal rhythm of 3OST2 expression was found in other tissues (data not shown). In the pineal significant expression was first detectable during the first hour after the lights-on and remained high throughout the daylight period and initial 2–3 h of the dark period (Fig. 1B). Transcript levels fell coincident with NAT activation and...
were dramatically down-regulated to undetectable levels during peak period of NAT gene expression (middle panel) and melatonin production (data not shown). The daytime-specific expression of 3OST2 was developmentally regulated (Fig. 1C) and first appeared between postnatal days 5 and 10, coinciding with the developmental onset of melatonin daily rhythms (17) and lagging behind the appearance of the NAT RNA rhythm (postnatal day 2 or earlier (14)).

3OST2 Expression Is Controlled by a Central Clock via the SCG and Is Light-inducible at Night—Temporal expression of 3OST2 was examined in pineals of rats maintained in constant light or dark conditions. The circadian expression of 3OST2 was maintained in constant dark, suggesting that it is under a central clock control (Fig. 2A). Continuous light exposure, which abolishes melatonin production and expression of all pineal night-specific genes including NAT, PINA, and Patched 1, up-regulates the 3OST2 transcription in the rat pineal (Fig. 2B). The time course of 3OST2 light induction (Fig. 2C) indicates that the 3OST2 expression is detectable within 2 h of light exposure and peaks at 8 h. The induction time course of 3OST2 expression corresponds with the inactivation of NAT transcription by light (middle panel in Fig. 2C). Bilateral ablation of the SCG, which suppresses NAT, restores 3OST2 expression at night (Fig. 2D).

β-Adrenergic Signaling Blocks 3OST2 Expression—We next correlated variations in 3OST2 gene expression with melatonin production in vivo in the presence of β-adrenergic agonist and antagonist. We first performed microdialysis on individual rats until their melatonin secretion patterns stabilized, which normally took 24 h after the beginning of on-line sampling (18). Rats were then given isoproterenol (ISO) or phosphate-buffered saline through either intraperitoneal injection or via the microdialysis probe. Rats injected with intraperitoneal phosphate-buffered saline showed no effect on melatonin formation or daytime expression of 3OST2, NAT, or TPH (tryptophan hydroxylase (a gene that does not diurnally vary) during the day (Fig. 3B). In contrast, intraperitoneal ISO injection abolished daytime 3OST2 expression, produced large increases of melatonin secretion, and increased NAT expression through the entire pineal (Fig. 3A). To demonstrate that ISO acts directly on pineal, we delivered the drug into the pineal through the microdialysis probe. Direct infusion of ISO into the pineal gland elevated melatonin production (Fig. 3C, upper panel)(145,905),(210,967) and blocked 3OST2 expression in areas immediately around the microdialysis membrane. This correlated spatially with areas of NAT transcriptional activation (Fig. 3C, lower panels). Propranolol (PROP), a potent β-adrenergic receptor antagonist infused directly into the pineal (Fig. 3D), activated 3OST2, suppressed NAT gene expression (lower panels), and completely abolished melatonin production (upper panel) in the same pineal gland.

Night Pineal Expression of 3OST2 Is Compatible with NAT Expression, Melatonin Production, and Light Responsiveness of Melatonin Formation—The expression patterns and regulatory mechanisms of 3OST2 are the exact opposite of those of NAT and melatonin production, suggesting that 3OST2 expression might be incompatible with melatonin synthetic pathways. To test this, rat pineals injected with AdCMV-3OST2::GFP were isolated 4 days after the injection during dark hours and sectioned for in situ analysis. As shown in Fig. 4A, NAT and TPH gene expression was not affected in areas expressing 3OST2. The effect of 3OST2 gene expression in the night pineals on melatonin secretion was monitored continuously in living rats for 5 days with or without light stimulation at night. At the end of the 5th day, rats were sacrificed at night, and pineals were sectioned and analyzed for expression of the recombinant 3OST2-expressing adenovirus using fluorescent microscopy and in situ hybridization (Fig. 4B). Melatonin secretion patterns of AdCMV-3OST2::GFP-injected rats (upper panel) are indistinguishable with that of animals injected with GFP-expressing virus (AdCMV-GFP, lower panel). A light pulse of 10 min, a known disrupter of melatonin formation at night, resulted in precipitous decline of melatonin secretion, which recovered shortly after, in both 3OST2- and GFP-expressing rat pineals (Fig. 4B). These in vivo studies indicate that 3OST2 does not antagonize melatonin synthesis.

**DISCUSSION**

Molecular mechanisms of circadian rhythm generation have been the subject of intense investigation. In this study we characterized the expression of 3OST2, a pineal daytime-specific transcript identified in the same subtractive screening that permitted isolation of NAT, PINA, and Patched 1 as light-responsive genes. In the pineal, β-adrenergic signaling suppresses and light activates 3OST2 gene expression. Although 3OST2

**Fig. 4.** Night expression of 3OST2 in the pineal does not antagonize NAT transcription, melatonin formation, or melatonin light responsiveness. A, NAT expression is normal in rats expressing 3OST2 at night. One to two µl of AdCMV-3OST2::GFP virus was injected directly into the living rat pineals using the surgical technique described (see “Experimental Procedures”). Four days after the procedure, the injected pineals were harvested at night (7 a.m.) for in situ analysis using 3OST2, NAT, and TPH ribo-probes. An adjacent section was also analyzed using fluorescent microscopy to demonstrate co-expressed GFP. B, 3OST2 expression does not disrupt melatonin production or its response to light stimulation at night. Rats injected with AdCMV-3OST2::GFP (upper panel) or AdCMV-GFP (lower panel) viruses were monitored for their melatonin output with or without a light pulse. A light pulse of 10 min was given to rats at 4 a.m. (arrows). Rats were sacrificed during the following night at 7 a.m., and pineals were analyzed for 3OST2 RNA (upper panel inset) or GFP (lower panel inset) expression.
message displays an opposite mode of regulation with all known night-specific pineal transcripts, 3OST2 night expression does not affect NAT gene expression and melatonin production.

Melatonin is a circadian hormone whose daily cycle is under strict clock control. Cyclic AMP signaling resulted from activation of pineal β-adrenergic receptor has been shown to be the primary local force behind the dynamic oscillation of melatonin formation. Because cAMP signaling in cell types other than the pineolocytes does not activate NAT and melatonin production, it is evident that other signaling molecules in the pineal gland are important to the generation of melatonin rhythm. Because melatonin formation itself is dynamically regulated at transcriptional level, we postulated that other factors that are crucial for melatonin rhythm also are controlled by rhythmic circadian gene activity. We therefore performed large scale screening of our subtracted pineal day and night cDNA library (12) and identified an additional few dozen night-specific and several day-specific clones. Here we demonstrate the utility of using an in vivo system to systematically analyze the function of one of these genes, 3OST2, a day-specific transcript in its natural contexts.

Analysis of mammalian gene function has traditionally been accomplished through germ line manipulation of mice via either gene knockout or transgenesis. Although these types of analysis typically provide useful information, they are not ideal for pineal studies due to the small size of the pineal gland and the fact that most mouse strains do not produce detectable levels of melatonin. Transgenic rat studies, although valuable for analyzing a couple of genes in detail, appear to be time-consuming and costly. In this study, we demonstrated the successful gene transfer into the living pineals by direct delivery of recombinant adenovirus that expresses genes of interests via surgery. Using a novel surgical approach, we were able to target viral vectors to the rat pineals with more than 90% accuracy. To delineate functional consequences of expressed genes on melatonin production in vivo, we integrated the pineal adenoviral gene expression technique with in vivo microdialysis approach, which permitted us to probe the functional relevance of 3OST2 to the melatonin output in living animals in real time. Final validation of accurate and high level infection is possible as shown by in situ hybridization at the conclusion of in vivo monitoring. Traditionally, pineal gene expression analysis and functional studies are performed in separate cohorts of animals. In this paper we integrated molecular analysis of pineal gene expression with physiological measurement of in vivo pineal melatonin output in the same individuals, which enabled us to obtain a comprehensive molecular understanding of pineal 3OST2 regulation. This novel approach can be particularly useful in situations where gene expression patterns need to be correlated with physiology in the same animals. We believe that these newly developed approaches should accelerate further understanding of functions of pineal diurnally expressed gene as well as mechanisms of their in vivo regulation.

3OST2 is the first day-specific transcript identified in the pineal gland. Because all the night-specific genes identified thus far are up-regulated by β-adrenergic signaling, we hypothesized that the day-specific 3OST2 regulation could be achieved by β-adrenergic receptor-controlled repression. We demonstrated that this prediction was indeed correct and that 3OST2 is activated by light stimulation and suppressed by β-adrenergic signaling. The identification of diurnally regulated genes whose expression and regulation complement those of pineal night-specific genes such as NAT, PINA, and patched 1 will undoubtedly facilitate understanding of the molecular mechanisms that govern the pineal circadian gene expression and melatonin production.

Recently, accumulating insights from genetic studies in Drosophila and mice have made it apparent that heparan sulfate proteoglycans formed by enzymes including sulfotransferases are critical in the interactions between specific extracellular ligands and their signal-transducing receptors (3). 3OST2 has been shown to sulfate precursor heparan sulfate at selective sites and, therefore, may generate glycosaminoglycans with targeting specificities different from that of 3OST1 or 3OST3 (7). It remains to be determined what receptor-ligand interactions are mediated by the enzymatic activities of 3OST2 and how it contributes to the pineal circadian physiology. Our demonstration that in vivo 3OST2 overexpression fails to affect melatonin production argues strongly for the existence of novel diurnal functions of the pineal.

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