Identification and Localization of a Skeletal Muscle Serotonin 5-HT_{2A} Receptor Coupled to the Jak/STAT Pathway*

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The neurotransmitter serotonin mediates a wide variety of peripheral and central physiological effects through the binding to multiple receptor subtypes (Wilkinson, L. O., and Dourish, C. T. (1991) in Serotonin Receptor Subtypes: Basic and Clinical Aspects (Peroutka, S. J., ed) Vol. 15, pp.147–210, Wiley-Liss, New York). Among them, serotonin 5-HT_{2A} receptors are known to activate the phospholipase C-β second messenger pathway (Peroutka, S. J. (1995) Trends Neurosci. 18, 68–69). We identified and localized in rat skeletal muscle myoblasts a functional serotonin 5-HT_{2A} receptor. This receptor was detected on the plasma membrane, in myoblasts, and at the level of T-tubules in contracting myotubes. Binding of serotonin to its receptor increases the expression of genes involved in myogenic differentiation. Unexpectedly, the 5-HT_{2A} receptor is able to activate another signaling pathway; it triggers a rapid and transient tyrosine phosphorylation of Jak2 kinase in response to serotonin. Jak2-auto-phosphorylation is followed by the tyrosine phosphorylation of STAT3 (signal transducers and activators of transcription) and its translocation into the nucleus. We also find that the 5-HT_{2A} receptor and STAT3 co-precipitate with Jak2, indicating that they are physically associated. We conclude that the serotonin 5-HT_{2A} receptor identified in skeletal muscle myoblasts is able to activate the intracellular phosphorylation pathway used by cytokines. The presence of serotonin receptors in T-tubules suggests a role for serotonin in excitation-contraction coupling and (or) an effect in skeletal muscle fiber repairing.

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that mediates diverse central and peripheral physiological responses by interacting with multiple serotonin receptor subtypes (1). The physiological effects of serotonin are mediated by at least four families of 5-HT receptors that have been distinguished pharmacologically, depending on the second messenger they are coupled to. The first family, including 5-HT_{1} and 5-HT_{2} receptor subtypes, interacts negatively with adenylate cyclase, whereas the second family (5-HT_{3}) is coupled to the activation of phospholipase C-β/protein kinase C. The 5-HT_{3} receptor is a ligand-gated ion channel, and the family including 5-HT_{4}, 5-HT_{5} and 5-HT_{7} receptor subtypes activates adenylate cyclase (2). The receptors of the 5-HT_{2} subfamily are implicated in many central physiological functions of serotonin, such as neuronal sensitivity to tactile stimuli and mediation of hallucinogenic effects of lysergic acid diethylamide, as well as in peripheral cardiovascular effects, e.g. contraction of blood vessels and shape change in platelets. The 5-HT_{2A} (formerly 5-HT_{1C}) receptor shares an overall 49% sequence identity with the 5-HT_{2C} (formerly 5-HT_{1C}) receptor, but they present different patterns of expression in the brain (3). Transfection of both 5-HT_{2C} and 5-HT_{2A} receptors in NIH3T3 fibroblasts results in cellular transformation and focus formation (3). The mouse 5-HT_{2B} receptor, mainly expressed in the cardiovascular system, gut, and developing brain (4), shares the highest degree of homology with the other 5-HT_{2B} receptors cloned from the rat fundus or from human libraries (5). The 5-HT_{2B} receptor has been classified as a ligand-dependent proto-oncogene, since its expression is necessary and sufficient to induce tumor formation in nude mice (6).

Serotonin 5-HT_{2A} receptors have been mainly localized in frontal cortex (3), blood platelets (7), and aortic smooth muscle cells (8). To date, serotonin receptors have never been isolated in skeletal muscle cells. The present study reports the identification and localization of a functional skeletal muscle serotonin 5-HT_{2A} receptor in rat fetal myoblasts. This receptor mediates the serotonin-induced up-regulation of the transcription factor myogenin, and the neuronal glucose transporter isoform GLUT3, both expressed during myogenic differentiation. Furthermore, we show that the skeletal muscle serotonin 5-HT_{2A} receptor is capable of stimulating the Jak/STAT pathway.

MATERIALS AND METHODS

Cells and Culture Conditions—Primary cultures of myoblasts from 19-day-old rat fetuses were grown as described previously (9) with the following modifications. Myoblasts were separated from muscle fibers by a treatment (20 min, 37 °C) with 0.15% protease (Sigma) in Ham's F-12 medium containing 10% fetal calf serum. Myoblasts were plated at a density of 1.5 × 10^{6} cells/ml on gelatin-coated flasks, in minimal essential medium/199 medium (2/1) containing 10% horse serum and 0.2% Matrigel (Becton-Dickinson). Serum and Matrigel were removed 24 h before the beginning of the experiments. Media were purchased from Life Technologies, Inc.; fetal calf serum and horse serum were obtained from Boehringer Mannheim.

Cloning of a cDNA Coding for a Skeletal Muscle 5-HT_{2A} Receptor—Using total RNA isolated from 3-day-cultured fetal myoblasts as a template, first strand cDNA was synthesized by reverse transcription, using a cDNA synthesis kit according to the manufacturer’s instructions (Perkin Elmer). For amplification of the cDNA fragments by the PCR, 21-mer oligonucleotide primers were designed, based on a portion of the third intracytoplasmic loop of the rat 5-HT_{2A} receptor cDNA (3) (GenBank™ accession no. M30705). Forward (sense) primer was 5'-ACC TAC TTC CTG ACT ATC AAG-3' (nucleotides 816–837). Reverse (antisense) primer was 5'-GCC CAG CAT CTT GCA GCG CTT-5' (nucleotides 1016–1037). PCR fragments were subcloned into the BamHI-EcoRI sites of a Bluescript pBS-SK(+) plasmid (Promega), amplified in...
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**RNA Extraction and Northern Blotting—** Myoblasts were treated with 5×10$^{-6}$ M serotonin hydrochloride (Sigma) in the presence of the 5-HT$_{2A}$ receptor antagonist ketanserin (10$^{-6}$ M) in some experiments (Research Biochemicals Inc.). Total RNA was extracted from the cells by the guanidine thiocyanate method (10), then electrophoresed and transferred as described previously (9). Northern blots were hybridized with $^{32}$P-labeled cDNA probing codes for GLUT3, GLUT1 (a gift of Dr. G. Bell, Howard Hughes Medical Institute, University of Chicago, Chicago, IL), myogenin (provided by Dr. W. Wright, Southwestern Medical Center, University of Texas, Dallas, TX), and serotonin 5-HT$_{2A}$ receptor (cDNA cloned by reverse transcription-PCR).

**Localization of the 5-HT$_{2A}$ Receptor by Immunofluorescence—** Fetal myoblasts were grown on gelatin-coated Permanox four-chamber slides (Lab-Tek, Nunc) for 3 days (fusing myoblasts) or 8 days (contracting myotubes) as described previously (9). The serotonin 5-HT$_{2A}$ receptor was detected using a monoclonal anti-5-HT$_{2A}$ receptor antibody (PharMingen). Cells were incubated overnight at 4 °C in diluted antibody (dilution 1/500 in PBS, 0.2% gelatin), then washed three times with PBS, and treated for 1 h with fluorescein isothiocyanate-conjugated sheep anti-mouse IgG (dilution 1/128, Sigma). The slides were mounted in a glycerol/PBS mounting medium (CityFluor), and confocal laser scanning microscopy was performed, using a Leica confocal imaging system (TCS-4D) and an immersion lens (63×, numerical aperture 1.4). Localization of the 5-HT$_{2A}$ receptor was then processed to produce single composite images (extended focus).

**Protein Phosphorylation and Co-precipitation Assays—** Myoblasts were exposed to 5×10$^{-8}$ M serotonin for 0, 1, 5, 15, 30, or 60 min in serum-depleted minimal essential medium/199 medium at 37 °C. Cells were scraped on ice in phosphate-buffered saline, then lysed for 1 h at 4 °C with agitation, in 500 µl of ice-cold lysis buffer (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 5 mM EDTA, 50 mM NaF, 50 mM Na$_3$P$_2$O$_7$, 1% Triton X-100, 0.4 mM Na$_2$VO$_4$, 1 mM phenylmethylsulfonyl fluoride (PMSF), 1 µM leupeptin, 2 µM pepstatin A, 0.5 µM 1-phenylalanine-2-carboxylic acid, 5 µM 1-phenylalanine-2-carboxylic acid, 1 µM o-propanol). The cell lysates were centrifuged at 15,000 rpm at 4 °C for 30 min, to remove insoluble material. Immunoprecipitation was performed overnight at 4 °C using 10 µg of anti-Jak2/protein A-agarose, or 5 µg of biotinylated anti-phosphotyrosine antibody (RC 20-B). Then the immune complexes were precipitated for 2 h at 4 °C by addition of protein A-Sepharose (Pharmacia), for anti-Jak2 antibody, or streptavidin immobilized on agarose (Pierce) for biotinylated anti-phosphotyrosine antibody. The immunoprecipitates were washed in cold lysis buffer, boiled in 2× Laemmli loading buffer, and separated on a 7.5% polyacrylamide–SDS gel, then transferred electrophoretically to nitrocellulose membranes. The membranes were blocked overnight at 4 °C with 5% nonfat dry milk in TBST buffer (10 mM Tris-HCl, pH 7.4, 75 mM NaCl, 1 mM EDTA, 0.1% Tween 20), or 3% bovine serum albumin in TBST buffer, for anti-phosphotyrosine antibody. Membranes were incubated with the relevant primary antibody, washed, incubated with peroxidase-conjugated secondary antibody, and washed again. Blots were developed using the ECL chemiluminescence reagents (Amersham).

**Nuclear Protein Extract Preparation—** Myoblasts were exposed to 5×10$^{-8}$ M serotonin for 0, 1, 5, 15, 30, or 60 min. Nuclei were isolated according to the protocol described by Shaprio et al. (11), with the following modifications. Cells were washed with ice-cold phosphate-buffered saline, recovered by scraping, then pelleted and resuspended in 300 µl of hypotonic buffer (10 mM Heps, pH 7.9, 0.1 M EDTA, 0.1 mM EGTA, 0.75 mM spermine, 0.15 mM spermidine, 10 mM KCl, 1 mM dithiothreitol, 0.5 mM PMSF, 0.5 µM leupeptin, 0.5 µM pepstatin A, 1% aprotinin). Cells were broken by 3 strokes of the tight pestle of a Dounce homogenizer, after addition of hypotonic buffer containing 10% Nonidet P-40. Sucrose buffer (500 mM Heps, pH 7.9, 0.2 M EDTA, 10 mM KCl, 1 mM dithiothreitol, 0.5 mM PMSF, 1 µM leupeptin, 2 µM pepstatin A, 0.5 µM o-propanol, 5 µM 1-phenylalanine-2-carboxylic acid, 67.5% (w/v) sucrose) was slowly added and the homogenate mixed with 2 strokes of the loose pestle of the homogenizer. After centrifugation (1 min at 12,000 × g, 4 °C), the nuclear pellet was resuspended in 10% glyceroe nuclear resuspension buffer. The nuclear resuspension was treated according to Shapiro. Nuclear proteins (40 µg) were electro-
expression, in 3-day-cultured myoblasts (data not shown). A time course of serotonin effect was performed after treatment of 3-day-cultured myoblasts with 5 × 10⁻⁶ M serotonin, for times ranging from 1.5 to 24 h. In control cells, GLUT3 mRNA expression increased transiently between day 3 and day 4, as expected (9). Nevertheless, a 2–3-fold increase in GLUT3 mRNA level was observed as soon as 1.5 h after addition of serotonin to the culture medium. The effect, maximal after 3 h, decreased to reach the control level after 9 h. A similar time course was observed on myogenin mRNA expression, whereas the ubiquitous glucose transporter isoform GLUT1 was quite unaffected (Fig. 1A).

Inhibition of Serotonin-induced mRNA Up-regulation—To determine if serotonin-induced up-regulation of mRNAs was mediated by the 5-HT₂A receptor, myoblasts were exposed to serotonin in the absence or presence of serotonin receptor antagonists, and Northern blots were hybridized with 5-HT₂A receptor, GLUT3 and myogenin cDNA probes. Within 6 h, serotonin induced a 5-fold increase in 5-HT₂A receptor mRNAs, and a 2–3-fold increase in GLUT3 and myogenin mRNAs (Fig. 1B). This effect was completely abolished in the presence of 1 µM ketanserin, a specific 5-HT₂A receptor antagonist (Fig. 1B), whereas zacopride, a 5-HT₂A inhibitor, was inefficient (data not shown). Taken together, these results show that serotonin is able to increase the expression of genes expressed during myogenic differentiation, through the skeletal muscle 5-HT₂A receptor.

Cellular Localization of the 5-HT₂A Receptor—Fetal myoblasts and contracting myotubes were stained for the serotonin 5-HT₂A receptor by immunofluorescence, and images were analyzed by confocal laser scanning microscopy. The 5-HT₂A receptor was localized on the plasma membrane, in fusioning myoblasts (Fig. 2a). Later on during myogenic differentiation, 5-HT₂A receptors appeared at the level of deep invaginations of the plasma membranes, the transverse tubules (T-tubules), in contracting myotubes (Fig. 2b–h). T-tubules are known to transmit the electrical impulses that trigger muscular contraction from the cell surface to the sarcoplasmic reticulum, and to facilitate the distribution of substrates to the myofibers (12). The presence of serotonin receptors in T-tubules of contracting myotubes suggests a role for serotonin in excitation-contraction coupling, and (or) a trophic role for the skeletal muscle fiber.

Co-precipitation of the 5-HT₂A Receptor with Jak2 Kinase—Serotonin increased gene expression through a very rapid transduction pathway, since a 1-min stimulation of myoblasts by serotonin was sufficient to induce a 50% increase in GLUT3 mRNA levels 3 h later (data not shown). The intracellular Jak/STAT pathway transduces very quickly the signal of many cytokines and peptide growth factors (13). Ligand binding rapidly triggers tyrosine phosphorylation of STATs (14, 15) by receptor-associated tyrosine kinases of the Jak family (16–18).

To investigate whether serotonin was able to stimulate the Jak/STAT pathway, myoblasts were incubated with serotonin for 0, 5, 15, 30, or 60 min, and the association of Jak2 with the 5-HT₂A receptor was assessed. Cell lysates from serotonin-treated myoblasts were immunoprecipitated with anti-Jak2 antibody, and, after SDS-PAGE electrophoresis, immunoblotted with anti-5-HT₂A receptor antibody. This antibody revealed in rat brain, used as a positive control, a strong band at 55 kDa, and a minor band at 58 kDa, probably due to post-translational modifications (glycosylation or phosphorylation) of the receptor. In myoblasts, a major band corresponding to 55 kDa was detected. The association of Jak2 with the 5-HT₂A receptor was observed within 5 min after addition of serotonin, and was maximal after 15 min (Fig. 3A).

Serotonin-induced Phosphorylation of Jak2 Kinase—To determine whether Jak2 auto-phosphorylation was induced by serotonin stimulation, Western blots of cell lysates were immunoblotted with anti-phosphotyrosine antibody, then stripped and reprobed with anti-Jak2 antibody (Fig. 3B, a). In a second protocol, cell lysates were immunoprecipitated with anti-Jak2 antibody, then immunoblotted with anti-phosphotyrosine antibody (Fig. 3B, b). Tyrosine phosphorylation of Jak2 was maximal after 30 min and then decreased until 60 min. These results show that the 5-HT₂A receptor cloned in skeletal muscle myoblasts is functional and activates a pathway never described for serotonin.

Phosphorylation of STAT Protein(s) Involved in Serotonin-
mediated Signal Transduction—The activation of Jak kinases leads to the recruitment and phosphorylation of STATs proteins (19, 20). To determine which STATs proteins were phosphorylated after serotonin treatment, cell lysates were immunoprecipitated with anti-phosphotyrosine antibody and then immunoblotted with monoclonal antibodies raised against STAT proteins. STAT1α/β (p91/84), STAT3 (p92), and STAT6 (interleukin-4-STAT) were expressed in fetal myoblasts (Fig. 4, A–C). A431 cells, stimulated for 5 min with epidermal growth factor (100 ng/ml), were used as a positive control for STAT1 and STAT3, and mouse 3T3 cells as a positive control for STAT6. Tyrosine phosphorylation of STAT3 occurred within 5 min of exposure of myoblasts to serotonin, and was maximal after 30 min (Fig. 4B). No tyrosine phosphorylation of STAT1 (Fig. 4A) or STAT6 (Fig. 4C) was observed. In our study, only STAT3 was tyrosine-phosphorylated in response to binding of serotonin to the 5-HT2A receptor.

Association of Jak2, 5-HT2A Receptor, and STAT3—To determine whether STAT3 was associated with the complex Jak2 kinase-5-HT2A receptor in response to serotonin stimulation, the same blot as in Fig. 3A was stripped and then immunoblotted with anti-STAT3 antibody. Serotonin induced the co-precipitation of STAT3 with Jak2 within 5 min (Fig. 5A). The simultaneous co-precipitation of the 5-HT2A receptor and STAT3 with Jak2 suggests that STAT3 is associated to the receptor complex, in response to serotonin stimulation.

Nuclear Translocation of STAT3—The activated STATs dimerize and translocate to the nucleus, where they directly activate target genes (13). To test whether serotonin induced the nuclear translocation of STAT3 in myoblasts, cells were exposed to serotonin for 0, 1, 5, 15, 30, or 60 min, and nuclear protein extracts were electrophoresed. Western blots were immunoblotted with anti-STAT antibodies. Serotonin induced the nuclear translocation of STAT3 within 5 min, the presence of

Fig. 3. A, time course of the serotonin-induced association of Jak2 kinase with the 5-HT2A receptor (5-HT2A-R). Myoblasts were exposed to serotonin for 0, 5, 15, 30, or 60 min. Left panel, precipitated proteins: Jak2 immunoprecipitation (IP)/5-HT2A receptor immunoblotting (IB). Right panel, nonprecipitated proteins: 5-HT2A receptor immunoblotting. B, tyrosine phosphorylation of Jak2 kinase in response to serotonin. a, left panel, phosphotyrosine immunoprecipitation; right panel, same blot stripped and immunoblotted with Jak2. b, Jak2 immunoprecipitation/phosphotyrosine (PY) immunoblotting.

Fig. 4. Tyrosine phosphorylation of STAT3 in response to serotonin. Left panels, precipitated proteins; right panels, nonprecipitated proteins. A, left panel, phosphotyrosine immunoprecipitation/STAT1 immunoblotting; right panel, STAT1 immunoblotting. Control, epidermal growth factor-stimulated A431 cells. B, left panel, phosphotyrosine immunoprecipitation/STAT3 immunoblotting; right panel, STAT3 immunoblotting. Control, epidermal growth factor-stimulated A431 cells. C, left panel, phosphotyrosine immunoprecipitation/STAT6 immunoblotting; right panel, STAT6 immunoblotting. Control, mouse 3T3 cells. Abbreviations are as in Fig. 3 legend.

Fig. 5. A, co-precipitation of STAT3 with Jak2 kinase in response to serotonin. The blot showing 5-HT2A receptor-Jak2 kinase association (Fig. 3A) was stripped and reprobed with anti-STAT3 antibody. Left panel, precipitated proteins: Jak2 immunoprecipitation/STAT3 immunoblotting. Right panel, nonprecipitated proteins: STAT3 immunoblotting. B, nuclear translocation of STAT3. Nuclear proteins (40 μg) were immunoblotted with anti-STAT3 antibody. Abbreviations are as in Fig. 3 legend.
increases glucose transport rate and GLUT3 glucose transport for serotonin, in skeletal muscle fibers, since serotonin
This receptor is located at the level of T-tubules in contracting myotubes. The junctional T-tubules exert a dual role in muscle fibers, since they are involved both in facilitating substrate uptake, such as glucose (12), and excitation-contraction coupling. The presence of serotonin receptors in T-tubules underlies a trophic effect for serotonin, in skeletal muscle fibers, since serotonin increases glucose transport rate and GLUT3 glucose transporter expression in fetal myoblasts. Trophic effects of serotonin have already been described. Serotonin, detected early in embryonic development (21), plays a role in craniofacial (22) and cardiovascular morphogenesis (23, 24) by unknown molecular mechanisms. Some trophic functions of serotonin during embryogenesis have been related to the mitogenic and transforming properties of the 5-HT2B receptor (6). Nevertheless, the hypothesis that serotonin could play a role in excitation-contraction coupling must be considered.

The serotonin 5-HT2A receptor is a member of the G protein-linked receptor superfamily known to activate the phospholipase C-β/protein kinase C pathway (2). In fetal myoblasts, serotonin binding to the 5-HT2A receptor resulted in the stimulation of another signaling pathway, the Jak/STAT pathway. The serotonin-induced association of Jak2 to the 5-HT2A receptor allowed the recruitment of STAT3 to the receptor complex and its subsequent phosphorylation by the phosphorylated Jak2 kinase, and led to STAT3 nuclear translocation. A similar result was reported in human interleukin-6-treated NMCBT cells, where the rapid tyrosine phosphorylation of STAT3 correlated with the rapid tyrosine phosphorylation of STAT3, and the formation of STAT3-STAT3-DNA complexes (25). STAT3 was reported to increase the expression of genes that are expressed in response to tissue injury and inflammation, and are referred as acute phase response genes (26). Some fetal myoblasts persist in adult skeletal muscle as quiescent stem cells (muscle satellite cells) that are capable of differentiation to repair muscle fibers, in case of injury. In myoblasts, the nuclear translocation of STAT3, in response to serotonin, might be related to the up-regulation of myogenin, a transcription factor involved in myogenic differentiation. This point requires further studies.

The serotonin 5-HT2A receptor we cloned in skeletal muscle is the second member of the seven-transmembrane domain G protein-coupled receptor superfamily able to activate the Jak/STAT pathway, after the angiotensin AT1 receptor, in rat aortic smooth muscle cells (27, 28). It is noteworthy that contractions of rat aortic smooth muscle cells are stimulated by serotonin through 5-HT2A receptors. It could be of great interest to determine if serotonin stimulates also the Jak/STAT pathway in these cells. Recently, a mouse 5-HT2B receptor transfected in fibroblasts was reported to induce serotonin stimulation of mitogen-activated protein kinase cascade (ERK2/ERK1) through the Ras pathway (6). Furthermore, serine/threonine phosphorylation mediated by the mitogen-activated protein kinases was shown to play a role in the activation of STATs, linking STAT and Ras pathways (25, 29).

In conclusion, our results show that the Jak/STAT pathway is implicated in the serotonin-induced increase in mRNAs coding for proteins involved in myogenic differentiation, suggesting that this pathway may play a role in skeletal muscle ontogenesis, and (or) repairing. This novel localization and signal transduction for serotonin 5-HT2A receptors deserve further studies, in particular a search for implication of serotonin in excitation-contraction coupling.

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