ELSEVIER

The 5-HT1A Receptor: Signaling, Desensitization, and Gene Transcription

Paul R. Albert, Ph.D., Paola Lembo, B.Sc., John M. Storring, B.Sc., Alain Charest, M.Sc., and Caroline Saucier, B.Sc.

The hypothesis that antianxiety or antidepressant agents (e.g., 5-HT1A agonists, 5-HT uptake blockers) exert their clinical actions via enhancement of serotonergic neurotransmission due to desensitization of 5-HT1A autoreceptors predicts that regulation of this receptor plays a crucial role in the therapeutic actions of these agents. A multidisciplinary strategy is described for the characterization of the 5-HT1A receptor at the level of cellular signaling mechanisms and genetic regulation, using heterologous expression of the cloned receptor in cell lines, site-directed mutagenesis, isolation of receptor-positive neuronal cell lines, and promoter analysis of the 5-HT1A receptor gene. These analyses will yield new insights into the possible mechanisms down-regulation of 5-HT1A receptor signaling, and may suggest novel sites of inherent defect involved in anxiety syndromes or major depression. ***[Neuropsychopharmacology 14:19–25, 1996]***

KEY WORDS: *5-HT1A receptors; Antianxiety and antidepressant agents; Cellular signaling mechanisms; Major depression*

Serotonin uptake inhibitors (e.g., fluoxetine, paroxetine) and selective 5-HT1A receptor partial agonists (e.g., buspirone, ipsapirone) are effective in the treatment of major depression and generalized anxiety disorder but require several weeks of drug treatment to observe clinical improvement (Blier et al. 1990; Charney et al. 1990). Acting via distinct mechanisms, these compounds share the property of enhancing serotonergic neurotransmission by selectively downregulating 5-HT1A receptors located on the serotonergic cell body (Azmitia 1994). Serotonin 1A receptors act as inhibitory autoreceptors on serotonergic neurons of the raphe nuclei, whereas 5-HT1B receptors act as inhibitory presynaptic receptors at serotonergic nerve terminals. Both of these 5-HT receptors participate in a negative feedback loop to inhibit serotonergic activity (Figure 1).

From the Department of Pharmacology and Therapeutics, McGill University, Montreal, Canada H3G-1Y6.

Address correspondence to: Paul R. Albert, Department of Pharmacology and Therapeutics, McGill University, Montreal, Canada H3G-1Y6.

Received April 12, 1994; revised April 25, 1994; accepted May 3, 1994.

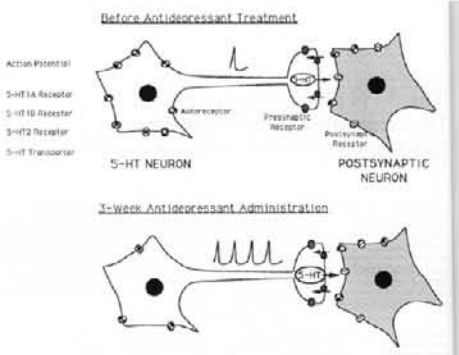
In experimental animals, long-term treatment with antidepressants induces selective loss of 5-HT1A autoreceptors without altering the responsiveness of postsynaptic 5-HT1A receptors (Welner et al. 1989; Blier et al. 1990; Fanelli and McMonagle-Strucko 1992). Uptake blockers may mediate this action due to chronic elevation of 5-HT levels at the synaptic cleft, leading to autoreceptor downregulation. Serotonin 1A receptor agonists appear to have a direct action on the autoreceptor to induce its desensitization. Desensitization of the autoreceptor disinhibits the serotonergic neuron, enhancing the rate of action potential firing to augment serotonergic neurotransmission. Increase in serotonergic neurotransmission correlates with the antidepressant or antianxiety activity of these therapeutic compounds. Interestingly, chronic enhancement of serotonergic neurotransmission induced by uptake blockers is potentiated by 5-HT1A receptor agonists, suggesting the importance of autoreceptor desensitization in antidepressant action (Hjorth 1993).

The cellular mechanisms involved in the longterm regulation of the 5-HT1A receptor remain uncharacterized, although the time course of therapeutic drug action suggests an effect of these compounds on gene transcription of components in the 5-HT1A receptor signaling system: either the receptor (Welner et al. 1989;

NEUROPSYCHOPHARMACOLOGY 1996—VOL. 14, NO. 1

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/96/$15.00
SSDI 0893-133X(94)00044-Z



1. Actions of long-term antidepressant drug treatment on pre- and postsynaptic 5-HT receptors. A schematic dia- depicts the receptors and spike activity of neurons in the central serotoninergic system before and after treatment n antidepressant drug (e.g., serotonin uptake blocker of 5-HT1A receptor agonist). Following 3-week antidepressant reatment, the most consistent changes observed include a decrease in 5-HT1A autoreceptors and consequent increase eurogic spike frequency and 5-HT release at the nerve terminal. Based on Blier et al., 1990.

li and McMonagle-Strucko 1992), G proteins h et al. 1991; Blier et al. 1993), or regulatory ki- /arrestins (Lefkowitz 1993). Neuron-specific differ- in the expression and regulation of these compo- may also explain the differential nature of receptor nitization, that is, that the 5-HT1A receptor desen- t in raphe but not in hippocampal neurons.

order to gain insight into the in vivo regulation 5-HT1A receptor, we have: (1) characterized the ns of the cloned 5-HT1A receptor; (2) undertaken tification of processes that regulate receptor func- and (3) characterized regulation of the receptor level of the gene. A variety of in vitro systems been developed to serve as accessible models for aracterization of the receptor (Albert 1994). Sev- ell lines have been transfected stably with the d 5-HT1A receptor, including pituitary GH4C1 nd fibroblasts Ltk- and Balb/c-3T3 cells (Albert et 90; Liu and Albert 1991; Abdel-Bauet et al. 1992) using methods previously described (Albert 1992). These cells have been used to characterize the cell-specific signal transduction of the receptor and its regulation. In addition, screening of RNA from neuronal cell lines by RT-PCR has led to the identification of the first neuronal cell line known to endogenously express the 5-HT1A receptor, the SN-48 septal-neuroblastoma hybrid (Charest et al. 1993). These cells can be used to characterize neuron-specific regulation and gene transcription of the receptor.

SIGNAL TRANSDUCTION

To modulate the activity of target neurons, many neurotransmitters (such as 5-HT) activate receptors that share a common structure with seven highly conserved alpha-helical transmembrane domains (Collins et al. 1991; Kobilka 1992). These receptors couple to hetero-

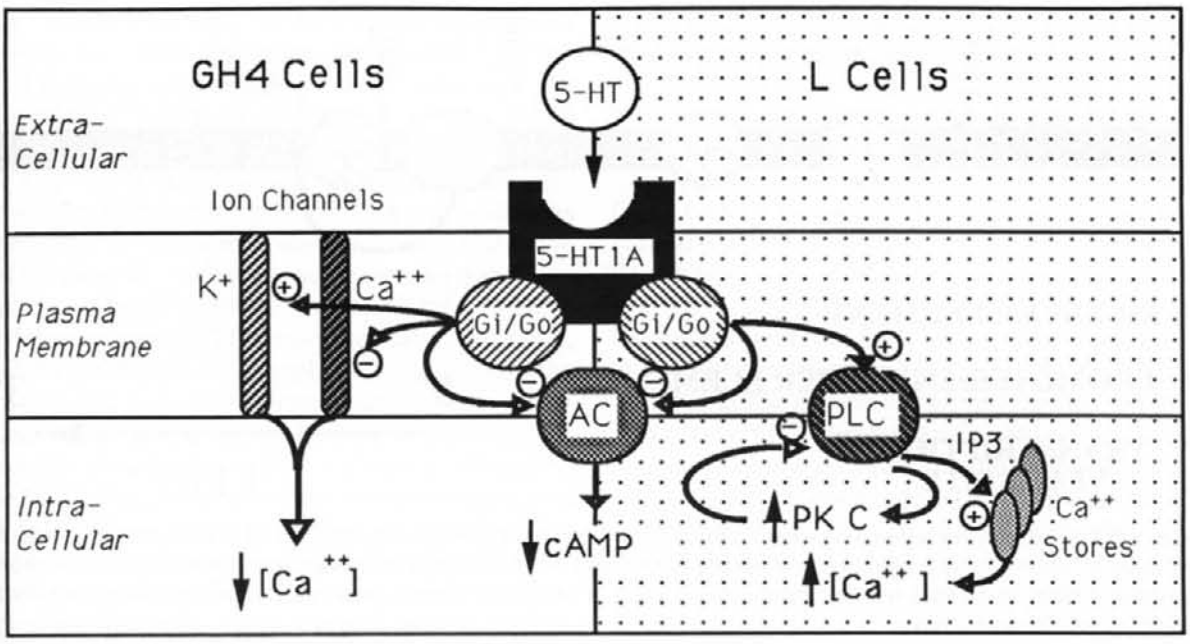


Figure 2. Cell-specific signaling of the 5-HT1A receptor. Agonist (5-HT)-induced activation of 5-HT1A receptors transfected into pituitary GH4 cells *decreases* $[Ca^{2+}]i$ by closing calcium channels and opening potassium channels; and *decreases* the intracellular level of cAMP by inhibiting both the basal and Gs-stimulated activity of adenylyl cyclase. In contrast, in transfected Ltk$^-$ fibroblast cells (L cells) the activated 5-HT1A receptor *increases* $[Ca^{2+}]i$ by enhancing PI turnover (via phospholipase C activation) to increase IP_3, which releases intracellular calcium stores; concomittant increase in DAG activates PK C, which negatively regulates the pathway possibly by phosphorylation of the receptor. In Ltk$^-$ cells 5-HT1A receptor-mediated inhibition of basal cAMP is not observed, but forskolin-induced cAMP accumulation is reduced. All receptor-induced actions are blocked by pretreatment with PTX, suggesting mediation by Gi/Go proteins.

trimeric G proteins that are composed of an α subunit GTPase and a βγ dimer (Birnbaumer et al. 1990; Birnbaumer 1992; Conklin and Bourne 1993). Multiple subtypes of α, β, and γ subunits have been identified, each of which interacts with specific effectors (e.g. adenylyl cyclase, phospholipase C, ion channels) to increase or decrease their activity and regulate neuronal activity. One subclass of G proteins, Gi/o proteins, is composed of αi/αo subunits that are rendered inactive by pretreatment with pertussis toxin (PTX), which catalyzes the ADP-ribosylation of these α subunits. The 5-HT1A receptor has been characterized biochemically and electrophysiologically as a receptor that couples to the Gi/o family of heterotrimeric G proteins, and to induce inhibition of neuronal activity (Innis et al. 1988; Zgombick et al. 1989; Pennington and Kelly 1990; Van den Hoof and Galvan 1992).

By stably transfecting the cloned 5-HT1A receptor into different receptor-negative cell lines, the cell-specific signal transduction of the receptor was identified (Fargin et al. 1989; Albert et al. 1990; Liu and Albert 1991; Abdel-Baset et al. 1992; Fowler et al. 1992). When transfected into pituitary GH4C1 cells, the cloned rat 5-HT1A receptor induces "inhibitory" responses typical of its neuronal signaling: inhibition of both basal and VIP-stimulated cAMP levels, closing of calcium channels, and no effect on PI turnover (Figure 2). Transfection of the receptor into L cells revealed agonist-dependent stimulation of phosphoinositide (PI) turnover to induce an immediate spike increase in cytosolic free calcium levels ($[Ca^{2+}]i$) via inositol trisphosphate (IP3)-mediated release of cellular calcium stores. Activation of the 5-HT1A receptor expressed in Balb/c-3T3 cells also induced PI turnover and increased $[Ca^{2+}]i$ analogous to the changes observed in L cells. In transfected fibroblast Ltk- or Balb/c-3T3 cells, the 5-HT1A receptor inhibited forskolin-stimulated cAMP synthesis but did not affect the basal cAMP level. All receptor-mediated changes in GH, L, and Balb/c-3T3 cells were prevented by pretreatment with PTX suggesting the involvement of Gi/Go proteins in both the stimulatory and inhibitory actions of the receptor.

The potential role of the "stimulatory" pathway of the 5-HT1A receptors in the regulation of cell proliferation was examined in nontransformed Balb/c-3T3 cells. Prolonged (16 hour) activation of the 5-HT1A receptor in growth-arrested Balb/c-3T3 cells was associated with increased DNA synthesis (as measured by ^{3}H-thymidine incorporation), which was abolished by pretreatment with PTX indicating mediation by Gi/Go proteins

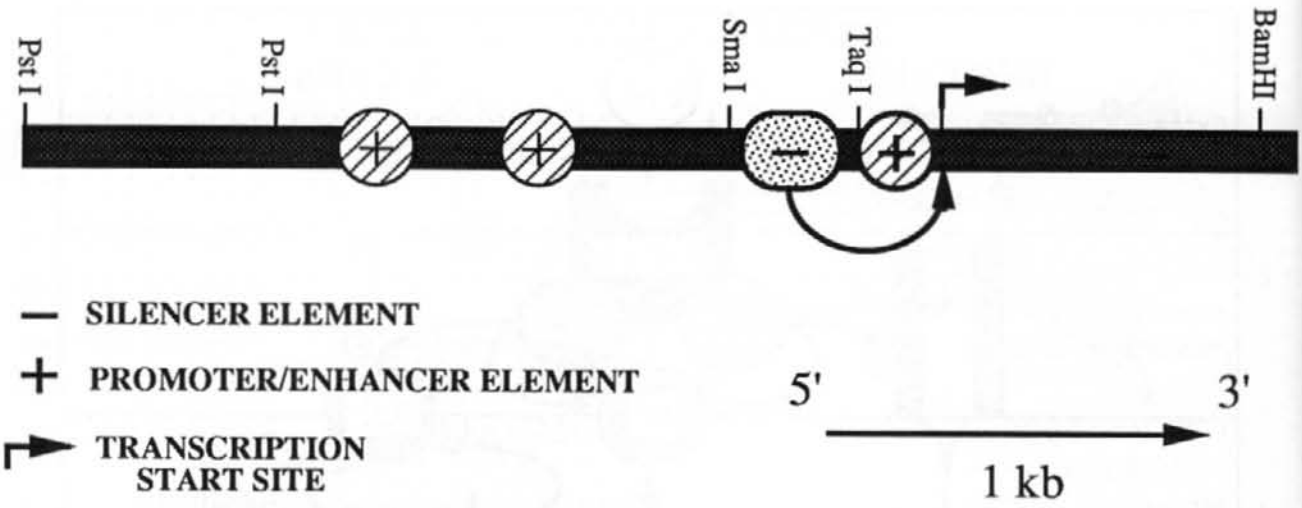


Figure 3. Promoter/silencer regions of the rat 5-HT1A receptor gene. The 5'-region of the rat 5-HT1A receptor gene is drawn to scale (arrow), ending at the initiation of translation at the right (3') end. The transcription start site and regions of promoter or repressor activity in transfected Ltk$^-$ and P19 cells are as indicated. Sites for cleavage of the gene by restriction endonucleases are also indicated.

(Abdel-Baset et al. 1992). Longterm treatment (1 to 2 weeks) of Balb/c-3T3 cells with 5-HT induced a PTX-sensitive morphological transformation and formation of foci of transformed cells. These results suggest that the stimulatory signals (e.g., stimulation of PLC and $[Cd^{2+}]i$) of the 5-HT1A receptor expressed in fibroblasts may serve to trigger cell growth and ultimately oncogenesis (Abdel-Baset et al. 1992). On the other hand, the inhibitory signals of the Gi/o-coupled dopamine-D2S receptor in transfected GH4ZR7 pituitary cells have been associated with inhibition of cell proliferation (Florio et al. 1992). Thus, alteration in receptor signaling from an inhibitory to a stimulatory phenotype may play a pivotal role in the control of cell growth, particularly if a given cell can be induced to "switch" from one signaling pathway to another. Interestingly, although the PI-linked receptor signal has not been described in neurons, a stimulatory 5-HT1A receptor signaling pathway is found in glial cells. Activation of endogenous 5-HT1A receptors enhances the secretion of S100 protein, which acts as a growth factor for serotonergic neurons (Whitaker-Azmitia 1991; Lauder 1993; Azmitia 1994), suggesting a role for stimulatory actions of the 5-HT1A receptor in enhanced neuronal growth and survival.

To define the biochemical basis for cell-specific receptor signaling, we have utilized an antisense approach to specifically knock out G proteins that may mediate 5-HT1A receptor actions (Albert 1994). Using stable transfection of expression vectors containing full-length antisense G protein α subunit cDNAs in the antisense orientation, we have achieved a complete and specific knockout of individual α subunits (Liu et al. 1994a). These knockouts indicate that in GH cells, Go couples multiple inhibitory receptors (including the 5-HT1A receptor) to inhibition of calcium channel opening, whereas the Gi proteins couple the receptor to inhibition of cAMP synthesis. Preliminary (transient expression) results in L cells indicate the Gi2 couples the 5-HT1A receptor to stimulation of $[Ca^{2+}]i$ levels. Thus, the same G protein (Gi2) induced an inhibitory cAMP signal in GH cells, but a stimulatory calcium signal in L cells, suggesting that the difference in signaling resides downstream from the G protein, perhaps involving cell-specific expression of different phospholipase C subtypes (Birnbaumer 1992).

DESENSITIZATION

Receptor desensitization as a result of sustained exposure to agonist has been best studied in the β-adrenergic receptor system and can result from receptor phosphorylation by receptor kinases (BARK) or other protein kinases, such as protein kinase A (PK A) or protein kinase C (PK C) (Kobilka 1992; Lefkowitz 1993). Desensitization of the 5-HT1A receptor occurs in vivo following prolonged elevation of 5-HT levels by uptake blockers or prolonged treatment with 5-HT1A agonists. Cell lines transfected with the receptor have provided models to study desensitization of the 5-HT1A receptor in vitro. Prolonged (24-hour) treatment of transfected Swiss 3T3 cells with 5-HT induces receptor desensitization (van Huizen et al. 1993), whereas acute (10-minute) treatment of transfected Hela cells leads to a 50% reduction in the number of 5-HT1A binding sites (Harrington et al. 1994). Desensitization in the latter case appears to be mediated in part by activation of PK C

via the PI-linked pathway of the 5-HT1A receptor. In transfected Ltk⁻ cells, a selective desensitization of the 5-HT1A receptor is induced by acute (2-minute) preactivation of PK C, which selectively abolished the PI and $[Ca^{2+}]i$ responses of the 5-HT1A receptor, but not the cAMP response (Liu and Albert 1991). Differential regulation of receptor signaling by PK C in Ltk⁻ cells was also observed for other receptors, including the dopamine D2S receptor, and to a lesser extent the dopamine D2L receptor (Liu et al. 1992). Since PK C induces phosphorylation of the 5-HT1A receptor (Raymond 1991), the role of specific PK C phosphorylation sites on the receptor in PK C–induced desensitization was examined. Site-directed mutagenesis of the receptor cDNA followed by transfection in Ltk⁻ cells revealed that no single PK C phosphorylation site mediated the action of PK C (Lembo et al. 1992). Although it is clear that PK C plays an important role in the desensitization process in these model cell lines, its role in agonist-induced receptor regulation in central nervous system will require the investigation of cells that endogenously express the receptor.

GENE TRANSCRIPTION

In order to examine its gene regulation, the 5′-flanking region of the rat 5-HT1A receptor gene was cloned and characterized (Charest and Albert 1994). Starting from the initiation of translation, we have used an RT-PCR approach to "walk" upstream along the gene and identify regions of transcriptional initiation. An intronless region 800 to 1000 bp upstream from the translational initiation was identified. Further primer extension studies with two different primers and RNAse protection studies confirmed the site of transcriptional initiation. DNA sequence analysis has revealed consensus sequences for a variety of transcription factors, which may play a role in the regulation of the gene. Several luciferase fusion constructs containing progressive deletions of the promoter region were made and transfected into receptor-negative cell lines (e.g., Ltk⁻ fibroblasts, P19 embryonal stem cells). A proximal promoter is flanked by a putative repressor region that is located upstream from the promoter and that inhibits receptor gene expression in these receptor-negative cells (Figure 3). Analogous repressor elements have been shown to regulate the neuron-specific expression of genes such as the type II sodium channel and SCG-10 genes, which are expressed in a wide variety of neurons (Wuenschell et al. 1990; Kraner et al. 1992; Mori et al. 1992). Although transfection of receptor-negative cells can be used to identify nonspecific promoter or repressor elements, the identification of promoter elements that regulate 5-HT1A receptor expression must be done in cells that normally express the receptor. However, receptor-bearing cell lines in which to study these promoter elements have yet to be identified.

The identification of 5-HT1A receptor-bearing cell lines is crucial to the understanding of the regulation of the gene by tissue- and neuron-specific factors, hormones (e.g. glucocorticoids), and second messengers (e.g., cAMP) that may play important roles in vivo (Chalmers et al. 1993; Mendelson and McEwen 1992; Beck 1994). Both septal and hippocampal cell lines have been screened by RT-PCR because these tissues express the highest levels of 5-HT1A receptor mRNA (Albert et al. 1990; Chalmers and Watson 1991; Pompeiano et al. 1992) and are likely to contain the highest proportion of receptor-expressing cells. We have identified a neuronal cell line generated by the fusion of mouse d21 septal cells with murine N18TG2 neuroblastoma cells (Lee et al. 1990a, 1990b) that endogenously expresses the 5-HT1A receptor, the SN-48 cells (Charest et al. 1993). These cells can be differentiated by addition of 10 µmol retinoic acid to medium containing 1% serum into cells that morphologically resemble neurons, and extent lengthy processes that contain neurofilament protein, a marker of neuronal processes. Upon differentiation of SN-48 cells with retinoic acid/low serum, the murine 5-HT1A receptor RNA was expressed, as identified by Northern blot analysis and by RT-PCR cDNA cloning and DNA sequencing of the 5-HT1A receptor mRNA in differentiated SN-48. Morphological differentiation and 5-HT1A receptor expression in SN-48 cells required concurrent addition of retinoic acid and low serum, whereas separate treatments were ineffective. These results indicate that the 5-HT1A receptor expression is not a direct action of retinoic acid, but required the retinoic acid-induced initiation of a differentiation program that included expression of the receptor. The receptor expressed in these cells is functional, and 5-HT addition induces inhibition of VIP- or PGE_2-stimulated cAMP synthesis in differentiated cells but not in nondifferentiated cells. These cells provide a neuronal cell model for investigating the desensitization and gene regulation of the 5-HT1A receptor.

CLOSING REMARKS

The hypothesis that antidepressant and anti-anxiety agents act to augment serotoninergic transmission by down-regulating inhibitory 5-HT1A autoreceptors in the raphe nuclei predicts that the regulation of this receptor plays a key role in depression and anxiety (Blier et al. 1990). A full understanding of the regulation of 5-HT1A receptor signaling should help elucidate the biochemical mechanisms involved in treatment for major depression and anxiety disorders, and may shed light on the etiology of these diseases.

ACKNOWLEDGMENTS

We acknowledge support from the Medical Research Council, Canada and the National Cancer Institute, Canada. PRA is Chercheur Boursier of the Fonds de la Recherche en Santé du Québec and JMS is a fellow of the Medical Research Council, Canada.

REFERENCES

Abdel-Baset H, Bozovic V, Szyf M, Albert PR (1992): Conditional transformation mediated via a pertussis toxin-sensitive receptor signalling pathway. Mol Endocrinol 6:730–740

Albert PR (1992): Molecular biology of the 5-HT1A receptor: Low-stringency cloning and eukaryotic expression. J Chem Neuroanat 5:283–288

Albert PR (1994): Heterologous expression of G protein-coupled receptors in endocrine and non-endocrine cell lines. Vitam and Horm 48:59–109

Albert PR, Zhou Q-Y, VanTol HHM, Bunzow J, Civelli O (1990): Cloning, functional expression, and mRNA tissue distribution of the rat 5-HT1A receptor gene. J Biol Chem 265:5825–5832

Azmitia E (1996): Neuropsychopharmacology 14:35–46.

Beck S (1996): Neuropsychopharmacology 14:27–33.

Birnbaumer L (1992): Receptor-to-effector signalling through G proteins: Roles for βγ dimers as well as α subunits. Cell 71:1069–1072

Birnbaumer L, Abramowitz J, Brown AM (1990): Receptor-effector coupling by G proteins. Biochim Biophys Acta 1031:163–224

Blier P, de Montigny C, Chaput Y (1990): A role for the serotonin system in the mechanism of action of antidepressant treatments; preclinical evidence. J Clin Psychiatry 54:14–21

Blier P, Lista A, de Montigny C (1993): Differential properties of pre- and postsynaptic 5-hydroxytryptamine 1A receptors in dorsal raphe and hippocampus: II. Effect of pertussis and cholera toxins. J Pharmacol Exp Ther 265:16–23

Chalmers DT, Watson SJ (1991): Comparative anatomical distribution of 5-HT1A receptor mRNA and 5-HT1A receptor binding in rat brain—a combined *in situ* hybridisation/*in vitro* receptor autoradiography study. Brain Res 561:51–60

Chalmers DT, Kwak SP, Mansour A, Akil H, Watson SJ (1993): Corticosteroids regulate brain hippocampal 5-HT1A receptor mRNA expression. J Neurosci 13:914–923

Charest A, Albert PR (1994): Promoter and silencer activities of the 5-HT1A receptor gene. Manuscript submitted

Charest A, Wainer BH, Albert PR (1993): Cloning and differentiation-induced expression of a murine serotonin1A receptor in a septal cell line. J Neurosci 13:5164–5171

Charney DS, Krystal JH, Delgado PL, Heninger GR (1990): Serotonin-specific drugs for anxiety and depressive disorders. Annu Rev Med 41:437–446

Collins S, Lohse MJ, O'Dowd B, Caron MG, Lefkowtiz RJ (1991): Structure and regulation of G protein-coupled receptors: The β-adrenergic receptor as a model. Vitam Horm 46:1–39

Conklin BR, Bourne HR (1993): Structural elements of Gα subunits that interact with Gβγ, receptors, and effectors. Cell 73:631–641

Fanelli RJ, McMonagle-Strucko K (1992): Alteration of 5-HT1A receptor binding sites following chronic treatment with ipsapirone measured by quantitative autoradiography. Synapse 12:75–81

Fargin A, Raymond JR, Regan JW, Cotecchia S, Lefkowtiz RJ, Caron MG (1989): Effector-coupling mechanisms of the cloned 5-HT1A receptor. J Biol Chem 264:14848–14852

Florio T, Pan M, Newman B, Hershberger RE, Civelli O, Stork PJS (1992): Dopaminergic inhibition of DNA synthesis in pituitary tumor cells is associated with phosphotyrosine phosphatase activity. J Biol Chem 267: 24169–24172

Fowler CJ, Ahlgren PC, Brännström G (1992): GH4ZD10 cells expressing rat 5-HT1A receptors coupled to adenylyl cyclase are a model for the postsynaptic receptors in the rat hippocampus. Br J Pharmacol 107:141–145

Harrington MA, Shaw K, Zhong P, Ciaranello RD (1994): Agonist-induced desensitization and loss of high-affinity binding sites of stably expressed human 5-HT1A receptors. J Pharmacol Exp Ther 268:1098–1106

Hjorth S (1993): Serotonin 5-HT1A autoreceptor blockade potentiates the ability of the 5-HT reuptake inhibitor citalopram to increase nerve terminal output of 5-HT in vivo: A microdialysis study. J Neurochem 60:776–779

Innis RB, Nestler EJ, Aghajanian GK (1988): Evidence for G protein mediation of serotonin- and $GABA_B$ induced hyperpolarization of rat dorsal raphe neurons. Brain Res 459:27–36

Kobilka B (1992): Adrenergic receptors as models for G protein-coupled receptors. Annu Rev Neurosci 15:87–114

Kraner SD, Chong JA, Tasy H, Mandel G (1992): Silencing the type II sodium channel gene: A model for neural-specific gene regulation. Neuron 9:37–44

Lauder JM (1993): Neurotransmitters as growth regulatory signals: Role of receptor and second messengers. TIPS 16:233–239

Lee HJ, Hammond DN, Large TH, Roback JD, Sim JA, Brown DA, Otten UH, Wainer BH (1990a): Neuronal properties and trophic activities of immortalized hippocampal cells from embryonic and young adult mice. J Neurosci 10:1779–1787

Lee HJ, Hammond DN, Large TH, Wainer BH (1990b): Immortalized young adult neurons from the septal region: Generation and characterization. Dev Brain Res 52:219–228

Lefkowtiz RJ (1993): G protein-coupled receptor kinases. Cell 74:409–412

Lembo P, Quik M, Albert PR (1992): Uncoupling of the rat serotonin1A receptor by a point mutation in the second cytoplasmic loop. Soc for Neuroscience, Anaheim, CA. Abstr 46.19, p 93

Lesch KP, Aulakh CS, Tolliver TJ, Hell JL, Murphy DL (1991): Regulation of G proteins by chronic antidepressant drug treatment in rat brain: Tricyclics but not clorgyline increase Goα. Eur J Pharmacol 207:361–364

Liu YF, Albert PR (1991): Cell-specific signalling of the 5-HT1A

receptor. Modulation by protein kinases C and A. J Biol Chem 266:23689–23697

Liu YF, Civelli O, Grandy DK, Albert PR (1992): Differential sensitivity of the short and long human dopamine-D2 receptor subtypes to protein kinase C. J Neurochem 59:2311–2317

Liu YF, Jakobs KH, Rasenick MM, Albert PR (1994a): G protein specificity in receptor-effector coupling. Analysis of the roles of Go and Gi2 in GH4C1 pituitary cells. J Biol Chem 269:13880–13886

Liu YF, Albert PR, Rasenick MM, Jakobs KH (1994b): Gi-coupled receptor-mediated stimulation of cAMP synthesis upon ablation of distinct Gαi gene expression. Manuscript submitted

Mendelson SD, McEwen BS (1992): Autoradiographic analysis of the effects of adrenalectomy and corticosterone on 5-HT1A and 5-HT1B receptors in the dorsal hippocampus and cortex of the rat. Neuroendocrinology 55:444–450

Mori N, Schoenherr C, Vandenberg DJ, Anderson DJ (1992): A common silencer element in the SCG10 and type II Na+ channel genes binds a factor present in nonneuronal cells but not in neuronal cells. Neuron 9:45–54

Pennington NJ, Kelly JS (1990): Serotonin receptor activation reduces calcium current in an acutely dissociated adult central neuron. Neuron 4:751–758

Pompeiano M, Palacios JM, Mengod G (1992): Distribution and cellular localization of mRNA coding for 5-HT1A receptor in the rat brain: Correlation with receptor binding. J Neurosci 12:440–453

Raymond JR (1991): Protein kinase C induces phosphorylation and desensitization of the human 5-HT1A receptor. J Biol Chem 266:14747–14753

Van den Hooff P, Galvan M (1992): Actions of 5-hydroxytryptamine and 5-HT1A receptor ligands on rat dorso-lateral septal neurones in vitro. Br J Pharmacol 106:893–899

van Huizen F, Bransse M, Stam NJ (1993): Agonist-induced down-regulation of human 5-HT1A and 5-HT2 receptors in Swiss 3T3 cells. Neuroreport 4:1327–1330

Welner SA, deMontigny C, Desroches J, Desjardins P, Suranyi-Cadotte BE (1989): Autoradiograhic quantification of serotonin1A receptors in rat brain following antidepressant drug treatment. Synapse 4:347–352

Whitaker-Azmitia PM (1991): Role of serotonin and other neurotransmitter receptors in brain development: Basis for developmental pharmacology. Pharmacol Rev 43:553–561

Wuenschell CW, Mori N, Anderson DJ (1990): Analysis of SCG10 gene expression in transgenic mice reveals that neural specificity is achieved through selective derepression. Neuron 4:595–602

Zgombick JM, Beck SG, Mahle CD, Craddock-Royal B, Maayani S (1989): Pertussis toxin-sensitive guanine nucleotide-binding protein(s) couple adenosine A1 and 5-hydroxytryptamine1A receptors to the same effector systems in rat hippocampus: Biochemical and electrophysiological studies. Mol Pharmacol 35:484–494