Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 488 (2004) 1–9
www.elsevier.com/locate/ejphar

Review

Contributions of 5-HT_{2C} receptors to multiple actions of central serotonin systems

Marco Giorgetti[1], Laurence H. Tecott*

Center for Neurobiology and Psychiatry, University of California, San Francisco School of Medicine, 401 Parnassus Avenue, San Francisco, CA 94143-0984, USA

Received 16 October 2003; received in revised form 23 December 2003; accepted 8 January 2004

Abstract

Insights into neural mechanisms through which central serotonin (5-HT) systems influence brain function may be gained by examining the contributions of individual 5-HT receptor subtypes. Significant attention has focused on the 5-HT_{2C} receptor subtype, which is abundantly expressed throughout the central nervous system and displays high-affinity interactions with a wide variety of psychiatric medications. Both pharmacological and genetic approaches to the analysis of 5-HT_{2C} receptor function reveal that it contributes substantially to the serotonergic regulation of a wide variety of behavioral and physiological processes. For example, significant inhibitory effects of 5-HT_{2C} receptor stimulation have been observed in both limbic and striatal dopamine pathways. These may contribute to the effects of experimental 5-HT_{2C} receptor manipulations on responses to psychostimulant, atypical antipsychotic and antidepressant drugs. Further evidence for a role of these receptors in affect regulation arises from recent findings that alterations in 5-HT_{2C} mRNA editing are observed in the brains of suicide victims with a history of depression and in animals exposed to antidepressant drug treatment. Finally, we will review a growing body of evidence indicating a role of 5-HT_{2C} receptors in the serotonergic regulation of energy balance. Pharmacological and genetic studies reveal these receptors to influence feeding, glucose homeostasis and the energy efficiency of physical activity.
© 2004 Elsevier B.V. All rights reserved.

Keywords: Serotonin; Dopamine; Psychostimulant; Antidepressant; Antipsychotic; Food intake; Obesity; Transgenic

1. Introduction

Attempts to uncover neural mechanisms through which brain serotonin systems influence behavior are complicated by the heterogeneity of the receptors through which serotonin acts. At least 14 distinct subtypes of serotonin (5-hydroxytryptamine; 5-HT) receptors are expressed within the central nervous system (Barnes and Sharp, 1999). They are highly diverse with regard to their structures, gene regulation, primary effector mechanisms, regional and subcellular expression patterns and physiological actions. However, the multiplicity of 5-HT receptors provides an opportunity for a fine functional dissection of brain serotonin systems, one receptor at a time. Progress in this area has been facilitated by the development of relatively selective pharmacological tools and by molecular genetic techniques enabling the generation of animals with planned 5-HT receptor gene mutations. This will be illustrated by a discussion of the contributions of a prominent central serotonin receptor subtype—the 5-HT_{2C} receptor—to the actions of serotonin.

2. The 5-HT_{2C} receptor subtype

The 5-HT_{2C} receptor was initially identified in the choroid plexus, as a receptor binding site exhibiting high affinity for 5-HT, mesulergine and lysergic acid diethylamide (LSD) and low affinity for ketanserin (Pazos et al., 1985; Yagaloff and Hartig, 1985). Its activation stimulates phosphatidylinositol (PI) turnover (Conn et al., 1986). Because the binding properties of this receptor appeared to resemble 5-HT_{1A} and 5-HT_{1B} sites more than 5-HT_2 (now designated 5-HT_{2A}) sites, its original designation was 5-HT_{1C}. Subsequently, the molecular cloning of the cDNA encoding this receptor revealed it to be a member of the superfamily of G-protein coupled receptors (Julius et al.,

* Corresponding author. Tel.: +1-415-476-7858; fax: 1-415-476-7838.
E-mail address: Tecott@itsa.ucsf.edu (L.H. Tecott).
[1] Current address: Tularik Inc., 1120 Veterans Boulevard, South San Francisco, CA 94080, USA.

0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.01.036

1988; Lubbert et al., 1987) highly related to the 5-HT_{2A} receptor subtype, with which it shares substantial amino acid identity (Julius et al., 1990). Their high level of homology is associated with very similar pharmacological binding profiles, so that 5-HT_{2C} receptors may have contributed to many of the pharmacological actions originally attributed to the 5-HT_{2A} subtype. Because the two receptors were clearly members of the 5-HT_2 subfamily the 5-HT_{1C} receptor was renamed 5-HT_{2C} (Barnes and Sharp, 1999). The gene encoding the 5-HT_{2C} receptor is X-linked in both humans and mice (Milatovich et al., 1992).

Interestingly, the 5-HT_{2C} receptor is the only known G-protein coupled receptor whose mRNA undergoes post-transcriptional editing to yield different receptor isoforms (Burns et al., 1997). Particular isoforms vary with regard to their central distribution and the extent to which they display constitutive activation. It has been shown that editing sites are located in the second intracellular loop, which contains a consensus sequence for G protein interaction (Burns et al., 1997; Niswender et al., 1999). It is therefore clear that changes in amino acid sequence at this level may affect coupling ability between the receptor and its G protein. In this regard, it was recently reported that depletion of serotonin increases expression of 5-HT_{2C} mRNA isoforms encoding receptors with higher sensitivity to serotonin (Gurevich et al., 2002). Accordingly, expression of these isoforms is reduced by treatment with the mixed 5-$HT_{2A/2C}$ receptor agonist 4-iodo-2,5-dimethoxyamphetamine (DOI) (Gurevich et al., 2002). These results indicate that mRNA editing may serve as a mechanism whereby 5-HT_{2C} receptor activity is stabilized in the face of changing synaptic serotonergic input.

In recent years, a number of relatively selective pharmacological agents with agonist or antagonist activity at 5-HT_{2C} receptors have been developed. These, along with the availability of mutant mice lacking functional 5-HT_{2C} receptors, have allowed investigators to better understand the functional roles of this receptor in the central nervous system. Unlike the 5-HT_{2A} and 5-HT_{2B} receptors, there is little evidence for expression of 5-HT_{2C} receptors outside the CNS (Barnes and Sharp, 1999; Julius et al., 1988). Studies utilizing radioligand binding and in situ hybridization assays have provided a detailed map of the regional distribution of 5-HT_{2C} receptors in the brain of different species, including man (Lopez-Gimenez et al., 2001; Mengod et al., 1990; Pasqualetti et al., 1999; Pompeiano et al., 1994). Although the highest density of 5-HT_{2C} receptors has been consistently found in the choroid plexus, the functional significance of these receptors remains to be determined. Within brain tissue, 5-HT_{2C} binding sites are widely distributed in neocortical areas, hippocampus, nucleus accumbens, amygdala, dorsal striatum and substantia nigra. An overlapping distribution of 5-HT_{2C} receptor mRNA and 5-HT_{2C} receptor binding sites has been observed in monkey brain indicating a potential somatodendritic localization of these receptors (Lopez-Gimenez et al., 2001). Interestingly, both 5-HT_{2C} receptor mRNA and immunoreactivity have been observed in the dorsal raphe nucleus, a region providing serotonergic innervation of much of the forebrain (Clemett et al., 2000; Wright et al., 1995).

3. Modulation of mesocorticolimbic dopamine system function by 5-HT_{2C} receptors

Several lines of evidence indicate that serotonin exerts both tonic and phasic modulation of central dopamine transmission via activation of 5-HT_{2C} receptors. Initial evidence of 5-HT_{2C} receptor-mediated modulation of mesolimbic dopamine transmission arose from the observation that m-chlorophenylpiperazine (m-CPP; a mixed 5-$HT_{1B/2B/2C}$ receptor agonist) strongly inhibited the firing rates of ventral tegmental area (VTA) dopamine neurons in anesthetized rats (Prisco et al., 1994). These effects of m-CPP were reversed by mesulergine, a compound with antagonist activity at 5-HT_{2C} receptors. The existence of a reciprocal modulation between central serotonergic and dopaminergic systems has been validated by the observation that in the ventral tegmental area (VTA), the origin of mesocorticolimbic dopaminergic pathways, as well as in the substantia nigra pars compacta (SNc), the origin of the dopaminergic nigrostriatal projection, serotonergic projections innervate dopaminergic neurons themselves, as well as other cell types, such as inhibitory γ-aminobutyric acid (GABAergic) neurons (Cameron et al., 1997; Erhardt et al., 1998; Herve et al., 1987; Trent and Tepper, 1991). In addition, serotonergic neurons originating in mesencephalic raphe nuclei also send efferents to brain areas innervated by dopamine systems, such as dorsal and ventral striatum and prefrontal cortex (Azmitia and Segal, 1978).

The synthesis of compounds with higher selectivity for the 5-HT_{2C} receptor subtype has aided pharmacological characterization of 5-HT_{2C} receptor function. For example, SB-206553 a mixed 5-$HT_{2C/2B}$ receptor antagonist with 160-fold selectivity over the 5-HT_{2A} site was shown to attenuate the hypolocomotion induced by acute administration of m-CPP in rats (Kennett et al., 1996). A structural modification of SB-206553 has led to the synthesis of SB-242084, which displays at least 100-fold selectivity for 5-HT_{2C} receptors relative to the 5-HT_{2A} and 5-HT_{2B} receptor subtypes (Bromidge et al., 1997). As for 5-HT_{2C} receptor agonists, m-CPP and, to a lesser extent, MK-212 have been employed to assess functional consequences of 5-HT_{2C} receptor stimulation. However, these compounds display considerable affinity for other serotonergic and non-serotonergic receptors. More recently, selective 5-HT_{2C} receptor agonists, such as Ro 60-0175 have been developed and tested in a number of preclinical studies.

The above-mentioned compounds have been used to examine 5-HT_{2C} receptor influences on central dopamine transmission. Systemic administration of SB-242084 was found to increase firing rates of VTA dopamine neurons in a

dose-dependent fashion (Di Matteo et al., 1999). Existence of a 5-HT_{2C} receptor-mediated modulation of dopamine neuronal activity was further confirmed by the ability of the selective 5-HT_{2C} receptor agonist Ro 60-0175 to depress VTA dopamine neuron firing rates. Furthermore, using in vivo microdialysis, SB-242084 was found to increase dopamine levels in nucleus accumbens and prefrontal cortex of anesthetized rats (Di Matteo et al., 1999; Gobert et al., 2000). Conversely, systemic administration of 5-HT_{2C} receptor agonists (MK-212 and m-CPP) significantly reduced both basal firing rate and total number of events in bursts as well as number of bursts of VTA dopamine neurons (Di Giovanni et al., 2000). These results indicate 5-HT_{2C} receptor-mediated inhibitory control of VTA dopamine neurons.

It has been found that 5-HT_{2C} receptor mRNA is expressed by GABAergic neurons but not by dopamine neurons within SNc and VTA (Eberle-Wang et al., 1997). This raises the possibility that inhibitory effects of 5-HT_{2C} receptor stimulation on central dopamine function may depend upon a 5-HT_{2C} receptor-mediated enhancement of VTA GABAergic inhibitory tone. In this regard, it has been shown that both $GABA_A$ and $GABA_B$ receptor subtypes mediate inhibition of midbrain dopamine neuronal function (Chen and Rice, 2002; Giorgetti et al., 2002; Westerink et al., 1996).

The proposed involvement of VTA GABAergic transmission in the inhibitory effects of 5-HT_{2C} receptor stimulation on central dopamine transmission, has been substantiated by a study in which systemic as well as microiontophoretic administration of m-CPP excited VTA non-dopamine (GABAergic) neurons (Di Giovanni et al., 2001). Interestingly, recent experimental evidence indicates that approximately 60% of VTA mesoprefrontal projections are GABAergic (Carr and Sesack, 2000). Activation of mesoprefrontal GABAergic pathways could therefore play an important role in modulating excitatory outputs to sub-cortical structures. In this regard, we may speculate that 5-HT_{2C} receptor activation of VTA GABAergic neurons may actually inhibit dopaminergic neuronal activity via a long feedback loop involving glutamatergic pyramidal cells located in prefrontal cortex.

4. Role of 5-HT_{2C} receptors in the modulation of nigrostriatal dopamine transmission and basal ganglia function

Although electrophysiological data support a preferential control of mesocorticolimbic dopamine pathways by the 5-HT_{2C} receptor subtype (Di Matteo et al., 1999), biochemical studies indicate that pharmacological manipulation of the 5-HT_{2C} receptor significantly affects dopamine transmission in the dorsal striatum (Di Giovanni et al., 1999). It has been shown that 5-HT_{2C} receptors provide excitatory drive to projection neurons in the output regions of the basal ganglia (e.g. substantia nigra pars reticulata-SNr. (Rick et al., 1995)). The excitatory effects of 5-HT_{2C} receptors on basal ganglia ouput pathways are demonstrated by studies in which blockade of these receptors increases locomotion or enhances the actions of dopamine replacement therapy. For example, intracerebral infusion of the selective 5-HT_{2C} receptor antagonist SB 206553 into SNr has an antiparkinsonian action in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease (Fox et al., 1998). Moreover, systemic administration of SB 206553 potentiated the antiparkinsonian action of the dopamine D2 receptor agonist quinpirole in the 6-hydroxydopamine-lesioned rat, suggesting a treatment strategy for alleviating Parkinson's-related motor dysfunction. More recently, 5-HT_{2C} receptor binding was found to be increased in the output regions of the basal ganglia in Parkinson's disease patients with levodopa-induced dyskinesia, suggesting a compensatory up-regulation of receptor levels in response to decreased stimulation by endogenous transmitter (Fox and Brotchie, 2000). This led to speculation that a reduction in 5-HT_{2C} receptor transmission in basal ganglia output nuclei could contribute to levodopa-induced dyskinesia. Pharmacological agents that selectively stimulate 5-HT_{2C} receptors in output regions of the basal ganglia might therefore ameliorate the motor dyskinesias that frequently accompany levodopa therapy.

5. Role of 5-HT_{2C} receptors in modulating behavioral and neurochemical effects of drugs of abuse

All major drugs of abuse, including psychomotor stimulants and opiates, are believed to exert their rewarding effects through facilitation of mesolimbic dopamine transmission. For example, cocaine increases dopamine availability in the synapse by blocking the transporter mediating dopamine reuptake into the presynaptic terminal (Uhl et al., 2002), while morphine induces excitation of mesolimbic dopamine neurons primarily through a reduction of GABAergic inhibition of dopaminergic cells (Kornetsky and Duvauchelle, 1994). It is therefore clear that pharmacological agents influencing dopamine transmission could potentially modulate reinforcing and behavioral effects of drug of abuse. In this regard, much attention has been focused on those 5-HT receptor subtypes that are known to modulate mesolimbic dopamine function, such as the 5-HT_{2C} receptor.

For example, the 5-HT_{2C} receptor antagonist SB-206553 has been observed to alter cocaine-induced hyperactivity in a dose-dependent manner (McCreary and Cunningham, 1999). Whereas high doses augmented cocaine's effects on locomotor activity, lower doses actually attenuated behavioral activation. The authors discuss the ability of the high dose of SB-206553 to increase cocaine-induced behavioral activation as result of a drug-induced disinhibition of mesoaccumbens dopamine pathway, while inhibitory effects of lower doses of SB-206553 could result from a

preferential antagonism at the 5-HT_{2B} receptor subtype. More recently, hyperactivity induced by systemic injection of cocaine was attenuated by local administration of the 5-HT_{2C} receptor antagonist RS 102221 bilaterally into the shell of the nucleus accumbens, while administration of the same compound into the VTA did not affect cocaine-induced hyperactivity (McMahon et al., 2001). These results indicate that 5-HT_{2C} receptor activation may exert facilitatory effects on dopamine function in the nucleus accumbens. Additional evidence indicates that 5-HT_{2C} receptors located in distinct brain regions may produce opposing effects on behavioral responses to psychostimulant drugs. Direct stimulation of central 5-HT_{2C} receptors by Ro 60-0175 disrupted both cocaine and food maintained behaviors in an equivalent fashion (Grottick et al., 2000). Interestingly, suppressive effects of Ro 60-0175 on cocaine and food maintained behaviors were obtained with doses that did not alter spontaneous motor activity, and were prevented by co-administration of the potent 5-HT_{2C} receptor antagonist SB 242084. These results indicate that inhibitory effects of Ro 60-0175 on VTA dopamine neurons can account for the reduced reinforcing value of cocaine and food. This would contrast with the putative enhancement of dopaminergic neurotransmission produced by 5-HT_{2C} receptors within the nucleus accumbens.

In line with these findings, our laboratory has recently demonstrated that mice lacking functional 5-HT_{2C} receptors are more sensitive to the effects of acute cocaine on both locomotor activity and on nucleus accumbens dopamine levels (Rocha et al., 2002). Moreover, when trained to self-administer cocaine under a progressive ratio paradigm, mutant mice reach higher break points than their wild type controls; indicating that cocaine has greater reinforcing properties in 5-HT_{2C} receptor mutant mice. A potentially related phenotypic trait of 5-HT_{2C} receptor mutant mice is their enhanced locomotor activation in response to novelty. Mutant mice display reduced habituation to a novel environment, a behavioral trait that correlates with enhanced mesolimbic dopamine function as well as with higher propensity to self-administer cocaine (Marinelli and White, 2000). This seems to suggest that in 5-HT_{2C} receptor mutant mice, disinhibited mesolimbic dopamine transmission could represent a common neurobiological substrate for both increased sensitivity to cocaine as well as enhanced reactivity to a novel environment.

6. Role of 5-HT_{2C} receptors in the therapeutic effects of antidepressants

Selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine are used in first-line medical treatment for major depression (Vaswani et al., 2003). It is generally believed that antidepressant effects of this class of drugs depend on their ability to raise levels of synaptic serotonin. SSRIs have a delayed onset of action (usually 2–6 weeks) and may be accompanied by a number of unwanted side effects such as insomnia, anxiety, gastrointestinal disturbances and sexual dysfunction. It is still unknown which neurobiological processes underlie this delayed onset of antidepressant action. It has been proposed that inhibition of serotonin re-uptake by SSRIs activates presynaptic 5-HT_{1A} receptors on serotonergic cell bodies in the dorsal and median raphe. This inhibits the firing of serotonin neurons, thus reducing rather than increasing synaptic serotonin release (Artigas et al., 1996). The desired effect is an increased activation of postsynaptic 5-HT receptors, but this is not achieved until presynaptic 5-HT_{1A} become desensitized. This has led to a strategy involving coadministration of SSRIs with 5-HT_{1A} receptor antagonist. In accord with this, evidence exists that the nonspecific 5-HT_{1A} antagonist pindolol may improve antidepressant action (Artigas et al., 2001). However, affinity of this drug for other receptors (e.g. β-adrenoreceptors) raises the possibility that the observed effects could depend on pharmacological blockade of other targets.

Several lines of evidence indicate that 5-HT_{2C} receptor antagonists may be used to augment the efficacy of SSRIs. A number of tricyclic antidepressants and fluoxetine directly interact with 5-HT_{2C} receptors. Fluoxetine was found to inhibit the membrane currents elicited by serotonin in frog's oocytes expressing both cloned and rat 5-HT_{2C} receptors (Ni and Miledi, 1997). The affinity of fluoxetine for 5-HT_{2C} receptors was observed to be similar to its affinity for the serotonin transporter. Other SSRIs, like paroxetine, do not show appreciable antagonist effects at the 5-HT_{2C} receptor site. However, chronic paroxetine treatment was found to significantly attenuate the inhibitory effect of m-CPP. These results indicated that chronic SSRI treatment may lead to a functional desensitization of 5-HT_{2C} receptors. Such a reduction of 5-HT_{2C} receptor function may contribute to the antidepressant efficacy of SSRIs, as indicated by a recent study demonstrating that the acute antidepressant-like behavioral effects of imipramine are augmented by pretreatment with SB-206553 (Yamada and Sugimoto, 2001).

Another mechanism through which SSRIs may influence affective regulation involves their indirect effects on dopaminergic neurotransmission. Acute SSRI administration induces strong inhibition of VTA dopamine neuronal firing rates (Di Mascio et al., 1998). It was proposed that the inhibitory effect of the SSRIs on the activity of mesolimbic dopaminergic function might contribute to the lag in antidepressant action. Interestingly, inhibitory effects of acute fluoxetine treatment on VTA dopamine neuronal firing rates are prevented by pretreatment with the 5-HT_{2C} receptor antagonist mesulergine (Prisco and Esposito, 1995). Thus, full expression of antidepressant effects would depend, at least in part, upon a down-regulation/desensitization of 5-HT_{2C} receptors in the VTA. That, in turn, would promote dopamine function in the limbic system. This hypothesis is in accord with animal models of anhedonia such as amphetamine withdrawal, in

which decreased function of the mesoaccumbens dopamine pathway has been described (Markou et al., 1998).

Intriguing evidence also exists for a potential role of cortical 5-HT_{2C} receptors in the pathophysiology of depression. In a recent study, altered patterns of 5-HT_{2C} receptor editing were detected in post-mortem brains from suicide victims with a history of major depression (Gurevich et al., 2002). These changes were opposite to those detected in mice chronically treated with fluoxetine. Since different edited isoforms of 5-HT_{2C} receptors are associated with different levels of constitutive activity (Niswender et al., 1999), the authors conclude that a potential therapeutic effect of SSRIs could be to reverse abnormalities in 5-HT_{2C} receptor mRNA editing.

7. Role of 5-HT_{2C} receptors in the therapeutic effects of antipsychotic drugs

Drugs used for the treatment of psychotic states are typically considered to fall within two main classes: typical and atypical antipsychotics. Both classes of antipsychotics block dopamine D2 receptors to varying degrees. D2 receptor blockade is believed to account for much of the therapeutic efficacy of typical antipsychotics, such as chlorpromazine and haloperidol. However, these drugs are known to induce various extrapyramidal side effects, such as tardive dyskinesias. In contrast, treatment with atypical antipsychotics, such as clozapine and risperidone is associated with a significantly lower incidence of extrapyramidal side effects (Meltzer, 1999). Atypical antipsychotics display only weak affinity for D2 receptors, but high affinity for a variety of 5-HT receptor subtypes (i.e. 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7). These compounds display improved efficacy for treating negative symptoms of schizophrenia (Meltzer, 1999). The improved efficacy of these drugs has been proposed to relate to their high 5-HT_{2A}/D2 affinity ratio (Meltzer, 1999). However, in addition to the high affinity for the 5-HT_{2A} receptor subtype, atypical antispychotics such as clozapine and risperidone bind to the 5-HT_{2C} receptor subtype with submicromolar affinity (Canton et al., 1990; Roth et al., 1992). It is notable that a number of atypical antipsychotic drugs were found to decrease the basal formation of inositol phosphate in cells expressing rat or human 5-HT_{2C} receptors (Herrick-Davis et al., 2000). These results suggest that atypical antipsychotics could exert inverse agonist actions at 5-HT_{2C} receptors by reducing its levels of constitutive activity. In accord with this possibility, both clozapine and risperidone, but not haloperidol, were found to prevent the inhibitory effects of the 5-HT_{2C} receptor agonist Ro 60-0175 on nucleus accumbens dopamine release (Di Matteo et al., 2002).

A number of experimental reports have shown that administration of atypical antipsychotics preferentially increases dopamine extracellular levels in medial prefrontal cortex relative to nucleus accumbens and striatum (Kuroki et al., 1999; Moghaddam and Bunney, 1990). On the other hand, haloperidol significantly increases dopamine efflux from the nucleus accumbens, without affecting prefrontal cortical dopamine. The facilitatory effect of atypical antipsychotic drugs on mesocortical dopamine function has been associated with the ability of these drugs to improve negative symptoms of schizophrenia. In light of these findings, a possible involvement of 5-HT_{2C} receptors in mediating effects of atypical antipsychotics on mesocortical dopamine systems has been proposed (Di Matteo et al., 2002).

A side effect of treatment with antipsychotic drugs, particularly those of the atypical category, is increased body fat, which often leads to further morbidity and poor adherence to treatment. It has been recently shown that a specific polymorphism of the 5-HT_{2C} receptor regulatory region affects treatment-induced weight gain in first-episode schizophrenic patients (Reynolds et al., 2002). This suggests that altered 5-HT_{2C} receptor function could contribute to metabolic disorders often associated with antipsychotic medications.

8. Role of 5-HT_{2C} receptors in neural regulation of feeding and energy balance

For several decades, central serotonin systems have been implicated in the suppression of feeding behavior. Fenfluramine, a pharmacological agent with anorexic activity in rodents and humans (Foltin and Moran, 1989; McGuirk et al., 1991; Rogers and Blundell, 1979) globally and indirectly activates 5-HT receptors by stimulating synaptic release of serotonin and blocking its reuptake into presynaptic terminals (Rowland and Carlton, 1986). Conversely, treatments that suppress central serotonergic signaling produce hyperphagia and weight gain in humans and rodents (Blundell and Leshem, 1974; Geyer et al., 1976; Ghosh and Parvathy, 1973; Saller and Stricker, 1976).

A confluence of evidence strongly indicates that 5-HT_{2C} receptors contribute substantially to the serotonergic suppression of feeding. mCPP and the related nonspecific 5-HT receptor agonist trifluoromethylphenylpiperazine (TFMPP) produce hypophagia that is blocked by antagonists of the 5-HT_{2C} receptor (Kennett and Curzon, 1991; Kennett et al., 1997; Middlemiss and Tricklebank, 1992). The behavioral specificity of these agents and the more selective 5-HT_{2C} receptor agonist Ro 60-0175 has been investigated in ethological-influenced studies of feeding behavior. Similar effects on feeding behavior were noted, characterized by increases in the latency to feed and reductions of meal size (Clifton et al., 1993, 2000). The potential suitability of the 5-HT_{2C} receptor as a target for anorectic drug development was further highlighted by studies revealing that both pharmacological blockade and genetic inactivation of these receptors blunts the anorectic effects of dexfenfluramine (Vickers et al., 1999, 2001).

In accord with a role for 5-HT_{2C} receptors in the serotonergic suppression of feeding, a line of mutant mice lacking 5-HT_{2C} receptors were found to have elevations of body weight and adiposity relative to wild type littermates—the first reported instance of obesity arising from an engineered mutation (Tecott et al., 1995). Developmental studies of food intake revealed a chronic hyperphagia in the mutants beginning in the first 2 months of life and persisting through at least 1 year of age (Nonogaki et al., 1998). Interestingly, despite months of chronic hyperphagia, the body weights and adiposity levels of mutant mice did not diverge from those of wild type animals until 5–6 months of age. The hyperphagia of young adult mutant mice did not result from perturbations of leptin signaling-leptin levels and the acute feeding-suppressant response to exogenous leptin administration were normal in young adult mutants. Moreover plasma glucose, insulin, corticosterone, triglyceride and free fatty acid levels were normal in these animals.

In contrast, by 9–10 months of age, a transition to a different physiological state was apparent (Nonogaki et al., 1998). The body weights of mutants were elevated, accompanied by an increase in adiposity. In addition, older obese mutants displayed hyperinsulinemia, hyperleptinemia and partial resistance to exogenous leptin administration. The presence of a prediabetic state in older mutants was further indicated by elevations of fasting insulin levels, reduced glucose tolerance, and increase susceptibility to high fat diet-induced type 2 diabetes. A number of features of this obesity syndrome are reminiscent of common forms of human ‘‘middle-age’’ obesity. An understanding of the mechanisms through which the young adult mutants compensate for chronic hyperphagia and the subsequent age-related failure of those mechanisms may therefore shed light on this common human condition.

Because levels of food intake and locomotor activity were not observed to change during the period of obesity development, energy expenditure was examined using indirect calorimetry for metabolic rate determinations (Nonogaki et al., 2003). In young adult animals, no phenotypic differences were observed in total or in resting metabolic rate. However, older obese mutants displayed less total oxygen consumption relative to controls, without changes in resting metabolic rates. Surprisingly, simultaneous activity measurements revealed that the reduction in the total energy expenditure of mutants occurred despite twofold elevations of their locomotor activity levels. Correlational analysis of locomotor activity and oxygen consumption revealed that older obese mutants required less energy to travel a given distance than did age-matched wild type animals or younger mutants. Thus, as mutants enter the ‘‘middle-age’’ portion of their lifespan, a progressive reduction in the energy cost of physical activity may lead to a positive energy balance and fat accumulation. Future studies will determine whether such a phenomenon contributes to the age-related increases in the prevalence of human obesity, which doubles between the third and sixth decades of life (Flegal, 1996; Seidell and Flegal, 1997). Future studies will also examine the possibility that 5-HT_{2C} receptor agonists will reduce body weight by increasing the energy cost of physical activity, as well as by the suppression of food intake.

In light of the widespread central distribution of 5-HT_{2C} receptors, multiple candidate mechanisms for their effects on feeding exist. Particular attention has focused on the hypothalamus as the locus of serotonergic effects on feeding. Systemic administration of indirect agonists such as dexfenfluramine and fluoxetine increases extracellular hypothalamic serotonin levels, and microinjections of serotonin into the paraventricular nucleus (PVN) of the hypothalamus have been found to suppress feeding by reducing meal size and feeding rate (Hutson et al., 1988; Schwartz et al., 1989; Shor-Posner et al., 1986). Similar effects were also observed with microinjection of serotonin into the ventromedial (VMN) and dorsomedial (DMN) nuclei of the hypothalamus (Leibowitz et al., 1988). 5-HT_{2C} receptors are expressed in these and other hypothalamic regions implicated in the regulation of energy balance (Hoffman and Mezey, 1989; Wright et al., 1995).

Recent studies have reported an influence of 5-HT_{2C} receptors on hypothalamic melanocortin pathways (Heisler et al., 2002). 5-HT_{2C} receptors were found to be expressed in, and to activate, arcuate nucleus neurons expressing the melanocortin precursor proopiomelanocortin. These results raise the possibility that 5-HT_{2C} receptor-mediated activation of this pathway contributes to the anorectic effects of 5-HT_{2C} receptor stimulation. In accord with this, genetic and pharmacological melanocortin receptor antagonism was found to suppress anorectic effects of dexfenfluramine (Heisler et al., 2002). The extent to which 5-HT_{2C} receptors expressed in additional hypothalamic regions influence energy balance remains to be determined.

Furthermore, it remains possible that 5-HT_{2C} receptor expression at extrahypothalamic sites may also play a role in the serotonergic regulation of ingestive behavior. For example these receptors are expressed in the pontine lateral parabrachial nucleus, which has been implicated in the anorectic actions of mCPP and dexfenfluramine (Kaplan et al., 1998; Li et al., 1994; Wright et al., 1995). Additional sites of expression within the basal ganglia, amygdala and hippocampal formation also warrant consideration (Pazos and Palacios, 1985; Wright et al., 1995).

9. Conclusion

Twenty years after its initial identification as a distinctive serotonin binding site, the 5-HT_{2C} receptor has emerged as a prominent central nervous system serotonin receptor subtype. The pleiotropic effects of a 5-HT_{2C} receptor null mutation reflect roles for this receptor in the regulation of a wide variety of behavioral processes. The strong correlation of multiple mutant phenotypes with the effects of recently developed antagonist compounds provides compelling evi-

dence that the 5-HT_{2C} receptor contributes substantially to many physiological processes attributable to central serotonin function. Studies to date implicate the function of this receptor in the actions of a broad range of psychoactive compounds, including appetite suppressant, antidepressant, antipsychotic, anxiolytic, psychostimulant and psychedelic drugs. We anticipate that efforts currently underway to elucidate 5-HT_{2C} receptor function and the clinical efficacy of 5-HT_{2C} receptor-selective compounds will provide novel insights into the serotonergic regulation of behavior and the treatment of psychiatric disorders.

References

Artigas, F., Romero, L., de Montigny, C., Blier, P., 1996. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT1A antagonists. Trends Neurosci., 378–383.

Artigas, F., Celada, P., Laruelle, M., Adell, A., 2001. How does pindolol improve antidepressant action? Trends Pharmacol. Sci. 22, 224–228.

Azmitia, E.C., Segal, M., 1978. An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. J. Comp. Neurol. 179, 641–668.

Barnes, N.M., Sharp, T., 1999. A review of central 5-HT receptors and their function. Neuropharmacology 38, 1083–1152.

Blundell, J.E., Leshem, M.B., 1974. Central action of anorexic agents: effects of amphetamine and fenfluramine in rats with lateral hypothalamic lesions. Eur. J. Pharmacol. 28, 81–88.

Bromidge, S.M., Duckworth, M., Forbes, I.T., Ham, P., King, F.D., Thewlis, K.M., Blaney, F.E., Naylor, C.B., Blackburn, T.P., Kennett, G.A., et al., 1997. 6-Chloro-5-methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-indoline (SB-242084): the first selective and brain penetrant 5-HT2C receptor antagonist. J. Med. Chem. 40, 3494–3496.

Burns, C.M., Chu, H., Rueter, S.M., Hutchinson, L.K., Canton, H., Sanders-Bush, E., Emeson, R.B., 1997. Regulation of serotonin-2C receptor G-protein coupling by RNA editing [see comments]. Nature 387, 303–308.

Cameron, D.L., Wessendorf, M.W., Williams, J.T., 1997. A subset of ventral tegmental area neurons is inhibited by dopamine, 5-hydroxytryptamine and opioids. Neuroscience 77, 155–166.

Canton, H., Verriele, L., Colpaert, F.C., 1990. Binding of typical and atypical antipsychotics to 5-HT1c and 5-HT2 sites: clozapine potently interacts with 5-HT1c sites. Eur. J. Pharmacol. 191, 93–96.

Carr, D.B., Sesack, S.R., 2000. Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. J. Neurosci. 20, 3864–3873.

Chen, B.T., Rice, M.E., 2002. Synaptic regulation of somatodendritic dopamine release by glutamate and GABA differs between substantia nigra and ventral tegmental area. J. Neurochem. 81, 158–169.

Clemett, D.A., Punhani, T., Duxon, M.S., Blackburn, T.P., Fone, K.C., 2000. Immunohistochemical localisation of the 5-HT2C receptor protein in the rat CNS. Neuropharmacology 39, 123–132.

Clifton, P.G., Barnfield, A.M., Curzon, G., 1993. Effects of food deprivation and mCPP treatment on the microstructure of ingestive behaviour of male and female rats. J. Psychopharmacol., 7.

Clifton, P.G., Lee, M.D., Dourish, C.T., 2000. Similarities in the action of Ro 60-0175, a 5-HT2C receptor agonist and d-fenfluramine on feeding patterns in the rat. Psychopharmacology (Berl.) 152, 256–267.

Conn, P.J., Sanders-Bush, E., Hoffman, B.J., Hartig, P., 1986. A unique serotonin receptor in choroid plexus is linked to phosphatidylinositol turnover. Proc. Natl. Acad. Sci. U. S. A. 83, 4086–4088.

Di Giovanni, G., De Deurwaerdére, P., Di Mascio, M., Di Matteo, V., Esposito, E., Spampinato, U., 1999. Selective blockade of serotonin-2C/2B receptors enhances mesolimbic and mesostriatal dopaminergic function: a combined in vivo electrophysiological and microdialysis study. Neuroscience 91, 587–597.

Di Giovanni, G., Di Matteo, V., Di Mascio, M., Esposito, E., 2000. Preferential modulation of mesolimbic vs. nigrostriatal dopaminergic function by serotonin(2C/2B) receptor agonists: a combined in vivo electrophysiological and microdialysis study. Synapse 35, 53–61.

Di Giovanni, G., Di Matteo, V., La Grutta, V., Esposito, E., 2001. m-Chlorophenylpiperazine excites non-dopaminergic neurons in the rat substantia nigra and ventral tegmental area by activating serotonin-2C receptors. Neuroscience 103, 111–116.

Di Mascio, M., Di Giovanni, G., Di Matteo, V., Prisco, S., Esposito, E., 1998. Selective serotonin reuptake inhibitors reduce the spontaneous activity of dopaminergic neurons in the ventral tegmental area. Brain Res. Bull. 46, 547–554.

Di Matteo, V., Di Giovanni, G., Di Mascio, M., Esposito, E., 1999. SB 242084, a selective serotonin2C receptor antagonist, increases dopaminergic transmission in the mesolimbic system. Neuropharmacology 38, 1195–1205.

Di Matteo, V., Cacchio, M., Di Giulio, C., Di Giovanni, G., Esposito, E., 2002. Biochemical evidence that the atypical antipsychotic drugs clozapine and risperidone block 5-HT(2C) receptors in vivo. Pharmacol. Biochem. Behav. 71, 607–613.

Eberle-Wang, K., Mikeladze, Z., Uryu, K., Chesselet, M.F., 1997. Pattern of expression of the serotonin2C receptor messenger RNA in the basal ganglia of adult rats. J. Comp. Neurol. 384, 233–247.

Erhardt, S., Andersson, B., Nissbrandt, H., Engberg, G., 1998. Inhibition of firing rate and changes in the firing pattern of nigral dopamine neurons by gamma-hydroxybutyric acid (GHBA) are specifically induced by activation of GABA(B) receptors. Naunyn-Schmiedebergs Arch. Pharmakol. 357, 611–619.

Flegal, K.M., 1996. Trends in body weight and overweight in the U.S. population. Nutr. Rev. 54, S97–S100.

Foltin, R.W., Moran, T.H., 1989. Food intake in baboons: effects of a long-acting cholecystokinin analog. Appetite 12, 145–152.

Fox, S.H., Brotchie, J.M., 2000. 5-HT2C receptor binding is increased in the substantia nigra pars reticulata in Parkinson's disease. Mov. Disord. 15, 1064–1069.

Fox, S.H., Moser, B., Brotchie, J.M., 1998. Behavioral effects of 5-HT2C receptor antagonism in the substantia nigra zona reticulata of the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. Exp. Neurol. 151, 35–49.

Geyer, M.A., Puerto, A., Menkes, D.B., Segal, D.S., Mandell, A.J., 1976. Behavioral studies following lesions of the mesolimbic and mesostriatal serotonergic pathways. Brain Res. 106, 257–270.

Ghosh, M.N., Parvathy, S., 1973. The effect of cyproheptadine on water and food intake and on body weight in the fasted adult and weanling rats. Br. J. Pharmacol. 48, 328P–329P.

Giorgetti, M., Hotsenpiller, G., Froestl, W., Wolf, M.E., 2002. In vivo modulation of ventral tegmental area dopamine and glutamate efflux by local GABA(B) receptors is altered after repeated amphetamine treatment. Neuroscience 109, 585–595.

Gobert, A., Rivet, J.M., Lejeune, F., Newman-Tancredi, A., Adhumeau-Auclair, A., Nicolas, J.P., Cistarelli, L., Melon, C., Millan, M.J., 2000. Serotonin(2C) receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat. Synapse 36, 205–221.

Grottick, A.J., Fletcher, P.J., Higgins, G.A., 2000. Studies to investigate the role of 5-HT2C receptors on cocaine-and food-maintained behavior. J. Pharmacol. Exp. Ther. 295, 1183–1191.

Gurevich, I., Tamir, H., Arango, V., Dwork, A.J., Mann, J.J., Schmauss, C., 2002. Altered editing of serotonin 2C receptor pre-mRNA in the prefrontal cortex of depressed suicide victims. Neuron 34, 349–356.

Heisler, L.K., Cowley, M.A., Tecott, L.H., Fan, W., Low, M.J., Smart, J.L.,

Rubinstein, M., Tatro, J.B., Marcus, J.N., Holstege, H., et al., 2002. Activation of central melanocortin pathways by fenfluramine. Science 297, 609–611.

Herrick-Davis, K., Grinde, E., Teitler, M., 2000. Inverse agonist activity of atypical antipsychotic drugs at human 5-hydroxytryptamine2C receptors. J. Pharmacol. Exp. Ther. 295, 226–232.

Herve, D., Pickel, V.M., Tong, H.J., Beaudet, A., 1987. Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurons. Brain Res. 435, 71–83.

Hoffman, B.J., Mezey, E., 1989. Distribution of serotonin 5-HT1C receptor mRNA in adult rat brain. FEBS Lett. 247, 453–462.

Hutson, P.H., Donohoe, T.P., Curzon, G., 1988. Infusion of the 5-hydroxytryptamine agonists RU24969 and TFMPP into the paraventricular nucleus of the hypothalamus causes hypophagia. Psychopharmacology 95, 550–552.

Julius, D., MacDermott, A.B., Axel, R., Jessell, T.M., 1988. Molecular Characterization of a functional cDNA encoding the serotonin 1c receptor. Science 241, 558–564.

Julius, D., Huang, K.N., Livelli, T.J., Axel, R., Jessel, T.M., 1990. The 5HT2 receptor defines a family of structurally distinct but functionally conserved serotonin receptors. Proc. Natl. Acad. Sci. 87, 928–932.

Kaplan, J.M., Song, S., Grill, H.J., 1998. Serotonin receptors in the caudal brainstem are necessary and sufficient for the anorectic effect of peripherally administered mCPP. Psychopharmacology 137, 43–49.

Kennett, G.A., Curzon, G., 1991. Potencies of antagonists indicate that 5-HT1c receptors mediate 1-3(chlorophenyl) piperazine-induced hypophagia. Br. J. Pharmacol. 103, 2016–2020.

Kennett, G.A., Wood, M.D., Bright, F., Cilia, J., et al., 1996. In vitro and in vivo profile of SB 206553, a potent 5-HT2C/5-HT2B receptor antagonist with anxiolytic-like properties. Br. J. Pharmacol. 117, 427–434.

Kennett, G.A., Wood, M.D., Bright, F., Trail, B., Riley, G., Holland, V., Avenell, K.Y., Stean, T., Upton, N., Bromidge, S., et al., 1997. SB 242084, a selective and brain penetrant 5-HT2C receptor antagonist. Neuropharmacology 36, 609–620.

Kornetsky, C., Duvauchelle, C., 1994. Dopamine, a common substrate for the rewarding effects of brain stimulation reward, cocaine, and morphine. NIDA Res. Monogr. 145, 19–39.

Kuroki, T., Meltzer, H.Y., Ichikawa, J., 1999. Effects of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. J. Pharmacol. Exp. Ther. 288, 774–781.

Leibowitz, S.F., Weiss, G.F., Shor-Posner, G., 1988. Hypothalamic serotonin: pharmacological, biochemical, and behavioral analyses of its feeding-suppressive action. Clin. Neuropharmacol. 11, S51–S71.

Li, B.H., Spector, A.C., Rowland, N.E., 1994. Reversal of dexfenfluramine-induced anorexia and c-Fos/c-Jun expression by lesion in the lateral parabrachial nucleus. Brain Res. 640, 255–267.

Lopez-Gimenez, J.F., Mengod, G., Palacios, J.M., Vilaro, M.T., 2001. Regional distribution and cellular localization of 5-HT2C receptor mRNA in monkey brain: comparison with [3H]mesulergine binding sites and choline acetyltransferase mRNA. Synapse 42, 12–26.

Lubbert, H., Hoffman, B.J., Snutch, T.P., van Dyke, T., Levine, A.J., Hartig, P.R., Lester, H.A., Davidson, N., 1987. cDNA cloning of a serotonin 5-HT1C receptor by electrophysiological assays of mRNA-injected Xenopus oocytes. Proc. Natl. Acad. Sci. U. S. A. 84, 4332–4336.

Marinelli, M., White, F.J., 2000. Enhanced vulnerability to cocaine self-administration is associated with elevated impulse activity of midbrain dopamine neurons. J. Neurosci. 20, 8876–8885.

Markou, A., Kosten, T.R., Koob, G.F., 1998. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology 18, 135–174.

McCreary, A.C., Cunningham, K.A., 1999. Effects of the 5-HT2C/2B antagonist SB 206553 on hyperactivity induced by cocaine. Neuropsychopharmacology 20, 556–564.

McGuirk, J., Goodall, E., Silverstone, T., Willner, P., 1991. Differential effects of d-fenfluramine and d-amphetamine on the microstructure of human eating behavior. Behav. Pharmacol. 2, 113–119.

McMahon, L.R., Filip, M., Cunningham, K.A., 2001. Differential regulation of the mesoaccumbens circuit by serotonin 5-hydroxytryptamine (5-HT)2A and 5-HT2C receptors. J. Neurosci. 21, 7781–7787.

Meltzer, H.Y., 1999. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 21, 106S–115S.

Mengod, G., Nguyen, H., Le, H., Waeber, C., Lubbert, H., Palacios, J.M., 1990. The distribution and cellular localization of the serotonin 1C receptor mRNA in the rodent brain examined by in situ hybridization histochemistry. Comparison with receptor binding distribution. Neuroscience 35, 577–591.

Middlemiss, D.N., Tricklebank, M.D., 1992. Centrally active 5-HT receptor agonists and antagonists. Neurosci. Biobehav. Rev. 16, 75–82.

Milatovich, A., Hsieh, C.L., Bonaminio, G., Tecott, L.H., Julius, D.J., Francke, U., 1992. Serotonin receptor 1c gene assigned to X chromosome in human (band q24) and mouse (bands D-FG4). Hum. Mol. Genet. 1, 681–684.

Moghaddam, B., Bunney, B.S., 1990. Acute effects of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: an in vivo microdialysis study. J. Neurochem. 54, 1755–1760.

Ni, Y.G., Miledi, R., 1997. Blockage of 5HT2C serotonin receptors by fluoxetine (Prozac). Proc. Natl. Acad. Sci. U. S. A. 94, 236–240.

Niswender, C.M., Copeland, S.C., Herrick-Davis, K., Emeson, R.B., Sanders-Bush, E., 1999. RNA editing of the human serotonin 5-hydroxytryptamine 2C receptor silences constitutive activity. J. Biol. Chem. 274, 9472–9478.

Nonogaki, K., Strack, A., Dallman, M., Tecott, L.H., 1998. Leptin-insensitive hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene. Nat. Med. 4, 1152–1156.

Nonogaki, K., Abdallah, L., Goulding, E.H., Bonasera, S.J., Tecott, L.H., 2003. Hyperactivity and reduced energy cost of physical activity in serotonin 5-HT(2C) receptor mutant mice. Diabetes 52, 315–320.

Pasqualetti, M., Ori, M., Castagna, M., Marazziti, D., Cassano, G.B., Nardi, I., 1999. Distribution and cellular localization of the serotonin type 2C receptor messenger RNA in human brain. Neuroscience 92, 601–611.

Pazos, A., Palacios, J.M., 1985. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res. 346, 205–230.

Pazos, A., Hoyer, D., Palacios, J.M., 1985. The binding of serotonergic ligands to the porcine choroid plexus: characterization of a new type of serotonin recognition site. Eur. J. Pharmacol. 106, 539–546.

Pompeiano, M., Palacios, J.M., Mengod, G., 1994. Distribution of the serotonin 5-HT2 receptor family mRNAs: comparison between 5-HT2A and 5-HT2C receptors. Mol. Brain Res. 23, 163–178.

Prisco, S., Esposito, E., 1995. Differential effects of acute and chronic fluoxetine administration on the spontaneous activity of dopaminergic neurones in the ventral tegmental area. Br. J. Pharmacol. 116, 1923–1931.

Prisco, S., Pagannone, S., Esposito, E., 1994. Serotonin-dopamine interaction in the rat ventral tegmental area: an electrophysiological study in vivo. J. Pharmacol. Exp. Ther. 271, 83–90.

Reynolds, G.P., Zhang, Z.-J., Zhang, X.-B., 2002. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet 359, 2086–2087.

Rick, C.E., Stanford, I.M., Lacey, M.G., 1995. Excitation of rat substantia nigra pars reticulata neurons by 5-hydroxytryptamine in vitro: evidence for a direct action mediated by 5-hydroxytryptamine2C receptors. Neuroscience 69, 903–913.

Rocha, B.A., Goulding, E.H., O'Dell, L.E., Mead, A.N., Coufal, N.G., Parsons, L.H., Tecott, L.H., 2002. Enhanced locomotor, reinforcing, and neurochemical effects of cocaine in serotonin 5-hydroxytryptamine 2C receptor mutant mice. J. Neurosci. 22, 10039–10045.

Rogers, P.J., Blundell, J.E., 1979. Effect of anorexic drugs on food intake and the micro-structure of eating in human subjects. Psychopharmacology 66, 159–165.

Roth, B.L., Ciaranello, R.D., Meltzer, H.Y., 1992. Binding of typical and atypical antipsychotic agents to transiently expressed 5-HT1C receptors. J. Pharmacol. Exp. Ther. 260, 1361–1365.

Rowland, N.E., Carlton, J., 1986. Neurobiology of an anorectic drug: fenfluramine. Prog. Neurobiol. 27, 13–62.

Saller, C.F., Stricker, E.M., 1976. Hyperphagia and increased growth in rats after intraventricular injection of 5,7-dihydroxytryptamine. Science 192, 385–387.

Schwartz, D., Hernandez, L., Hoebel, B.G., 1989. Fenfluramine administered systemically or locally increases extracellular serotonin in the lateral hypothalamus as measured by microdialysis. Brain Res. 482, 261–270.

Seidell, J.C., Flegal, K.M., 1997. Assessing obesity: classification and epidemiology. Br. Med. Bull. 53, 238–252.

Shor-Posner, G., Grinker, J.A., Marinescu, C., Brown, O., Leibowitz, S.F., 1986. Hypothalamic serotonin in the control of meal patterns and macronutrient selection. Brain Res. Bull. 17, 663–671.

Tecott, L.H., Shtrom, S., Julius, D., 1995. Expression of a serotonin-gated ion channel in embryonic neural and non-neural tissues. Mol. Cell. Neurosci.

Trent, F., Tepper, J.M., 1991. Dorsal raphe stimulation modifies striatal-evoked antidromic invasion of nigral dopaminergic neurons in vivo. Exp. Brain Res. 84, 620–630.

Uhl, G.R., Hall, F.S., Sora, I., 2002. Cocaine, reward, movement and monoamine transporters. Mol. Psychiatry 7, 21–26.

Vaswani, M., Linda, F.K., Ramesh, S., 2003. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 27, 85–102.

Vickers, S.P., Clifton, P.G., Dourish, C.T., Tecott, L.H., 1999. Reduced satiating effect of d-fenfluramine in serotonin 5-HT2C receptor mutant mice. Psychopharmacology 143, 309–314.

Vickers, S.P., Dourish, C.T., Kennett, G.A., 2001. Evidence that hypophagia induced by d-fenfluramine and d-norfenfluramine in the rat is mediated by 5-HT2C receptors. Neuropharmacology 41, 200–209.

Westerink, B.H., Kwint, H.F., deVries, J.B., 1996. The pharmacology of mesolimbic dopamine neurons: a dual-probe microdialysis study in the ventral tegmental area and nucleus accumbens of the rat brain. J. Neurosci. 16, 2605–2611.

Wright, D.E., Seroogy, K.B., Lundgren, K.H., Davis, B.M., Jennes, L., 1995. Comparative localization of serotonin1A,1C, and 2 receptor subtype mRNAs in rat brain. J. Comp. Neurol. 351, 357–373.

Yagaloff, K.A., Hartig, P.R., 1985. 125I-lysergic acid diethylamide binds to a novel serotonergic site on rat choroid plexus epithelial cells. J. Neurosci. 5, 3178–3183.

Yamada, J., Sugimoto, Y., 2001. Effects of 5-HT(2) receptor antagonists on the anti-immobility effects of imipramine in the forced swimming test with mice. Eur. J. Pharmacol. 427, 221–225.