Role of the $5HT_{2c}$ receptor in regulation of metabolism and mesolimbic dopamine

Richard O'Neil

Serotonin (5HT) in the CNS plays an important role in regulation of behavioral and motivational states, and has an implied role in a number of behavioral pathologies including depression, schizophrenia, and drug abuse. 5HT acts in the CNS by binding receptors on the surface of neurons which then facilitate modulation of cellular processes and neuronal activity. The $5HT_{2c}$ receptor is a G-protein coupled receptor (GPCR) primarily expressed in the central nervous system. The $5HT_{2c}$ receptor is the only known GPCR subject to a form of post transcriptional modification known as RNA editing, a process in which specific adenosine residues are converted to inosine resulting in functional recoding of the mRNA. Editing of $5HT_{2c}$ receptor transcripts alters the functional signaling characteristics of the receptor, thus modulating the role the receptor plays in various neural processes. This review discusses evidence for the role of the $5HT_{2c}$ receptor in regulating feeding behavior, and mesoaccumbal dopamine signaling. Furthermore, it addresses the possible implications of dynamic RNA editing in these processes and discusses approaches to better understand the relationship *between* RNA editing and receptor function in vivo.

Neuroscience Graduate Program, Vanderbilt University School of Medicine, U1205 Medical Center North, Nashville, TN 37232, USA.
Correspondence e-mail: richard.t.oneil@vanderbilt.edu.

A fundamental requirement for the evolution of complex nervous systems is the capacity for plasticity at the molecular level. Enzymes, known as Adensosine Deaminases which Act on RNA (ADARs), have coevolved with nervous systems in many species to catalyze hydrolytic deamination of specific adenosine residues on RNA sequences, resulting in functional alteration of RNA transcripts[1]. In mammals, two genes have been shown to encode catalytically active ADARs (ADAR 1 and ADAR 2), and both are expressed in most tissues but are highly enriched in the CNS[2,3]. Through their ability to convert adenosines to inosines at specific residues on protein coding RNAs, ADARs have been shown to alter amino acid codons with profound functional implications in a number of genes. This recoding occurs because inosine is processed by the translational machinery as guanosine. This results in a functional coding alteration of A-to-G at edited residues[1]. Most of the characterized substrate RNAs modified by ADARs encode proteins associated with neuronal signaling. These include voltage gated and ligand gated ion channels[4,5], fast synaptic release machinery[6], and at least one G-protein coupled neurotransmitter receptor; the $5HT_{2c}$ receptor[7]. The necessity of ADAR activity for viability and nervous system function has been clearly demonstrated by a number of genetically modified mouse models in which activity of the respective ADARs or their editing activity on specific substrates has been disrupted[8,9,10].

RNA editing is a conserved mechanism allowing for precise and dynamic modulation of protein functions within the nervous system. This unique process provides insight into the critical aspects of protein function and makes it a powerful beacon to guide further scientific inquiry in molecular neuroscience. For example, the transcript encoding the serotonin 2c receptor ($5HT_{2c}$) can be edited at 5 adenosines in exon 5 of the mature mRNA. These sites are denoted A, B, E, C, and D sites respectively 5' to 3' (**Figure 1c**). Considerable differences in signaling properties have been observed *in vitro* for a number of the unique protein isoforms generated by different combinations of editing at these 5 sites. The functional differences result from modulation of three amino acid codons which genomically encode isoleucine-asperigine-isoleucine respectively at residues 156-158-160 located within the second intracellular loop of the mature receptor. Editing at these amino acid codons allows for the production of 24 unique protein isoforms which can differ by as few as one or as many as three amino acids[7] (**Figure 1**). The second intercellular loop of the receptor is known to be important for g-protein coupling and efficient activation of the $G_{q/11}$- phospholipase C beta (PLCβ) signaling cascade[11-13]. *In vitro* evidence suggests that protein isoforms generated by different combinations of editing at these three amino acid codons have profoundly altered properties with respect to trafficking and signaling efficacy [7,14,15,18]. Among the differences between edited isoforms is variability in ligand independent signaling capacity, termed constitutive activity. Constitutive activation of the

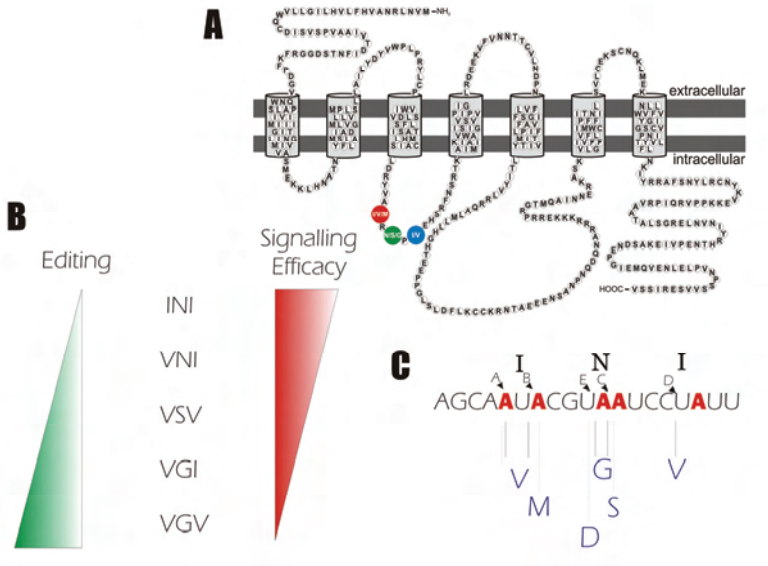

Figure 1 | **$5HT_{2c}$ isoforms. a |** Proposed 7TM domain structure and amino acid sequence of the Serotonin 2c receptor amino acids subject to aleration by editing shown in colored spheres. **b |** Schematic representation summarizing the relationship between editing and signaling efficacy of respective receptor isoforms. **c |** Pre-mRNA sequence of edited region showing editing sites and assigned names designated for each site. Single letter codes for amino acids encoded by non-edited transcript shown in black; amino acids encoded after editing at each position are indicated in blue.

$5HT_{2c}$ receptor has been observed in multiple cell lines transfected with transcripts encoding several different isoforms of the receptor [14,16,18]. Importantly, this constitutive activity is not detectable in cells expressing only the fully edited receptor isoform encoding valine-glycine-valine (VGV) and the activity is significantly reduced in isoforms encoded by more edited transcripts VNV and VSV[14]. With respect to ligand-dependant receptor activation, $5HT_{2c}$ receptor agonists have reduced signaling efficacy and affinity for isoforms encoded by more edited transcripts (**Figure 1b**). This reduction in agonist efficacy has been attributed to the existence of high and low affinity state receptors. According to the modified ternery complex model; receptors with constitutive activity fluctuate between inactive (R) and active (R*-G) conformations and the level of constitutive activity is a reflection of the relative time spent in R*-G state. Agonist binding promotes formation of R*-G complex and the affinity of an agonist is higher for the R*-G complex than for R. The more edited isoforms are less likely to achieve the R*-G complex in absence of agonist and therefore have reduced constitutive activity and exist predominately in a low affinity state[16]. The existence of multiple affinity states is supported by experiments in which non-hydrolysable GTP analogs are used to fully uncouple g-proteins (G) from the R-G complex, resulting in only low affinity state receptors[14,16]. The fact that all receptor isoforms tested can achieve similar maximal activation of PI hydrolysis suggests that the ability of $5HT_{2c}$ receptors to couple with g-proteins is not affected by editing and that signaling efficacy is primarily altered by ligand affinity and constitutive receptor activation[16]. While a great deal of progress has been made in characterizing the role of editing at this receptor for signaling in vitro, the role of distinct isoforms *in vivo* is not understood.

The $5HT_{2c}$ receptor has a broad expression profile in the CNS [17] and has been repeatedly implicated in the regulation of feeding behavior[20] and reward pathways[19]. Based on the *in vitro* data, the expression of distinct $5HT_{2c}$ receptor protein isoforms by RNA editing has the potential to profoundly affect the role of the receptor in these systems. This review will focus on recent work illuminating the role of the $5HT_{2c}$ receptor in the regulation of mesoaccumbal dopamine, as well as this receptor's role in regulating feeding behavior. Furthermore, it will discuss approaches to better characterize the distribution of edited isoforms in various cell types and brain regions. Finally, it will outline efforts to test the hypothesis that dynamic regulation of editing allows for precise modulation of behavior.

$5HT_{2C}$ RECEPTORS REGULATE METABOLISM AND FEEDING BEHAVIOR IN MICE

Regulating metabolism and feeding behavior is one of the most ubiquitous and fundamental functions facilitated by the mammalian nervous system. The brain maintains metabolic homeostasis through regulation of autonomic tone, glucose homeostasis, and by providing the motivational drive to consume food. The notion that 5HT plays an important role in the regulation of feeding became evident in the early 1970's when the drug fenfluramine came on the market for weight loss. The anorexigenic effects of fenfluramine have been attributed to its ability to increase extracellular 5HT levels[20]. Recent studies by Vickers et al, in which knockout mice lacking $5HT_{2c}$ receptors are treated with fenflouramine, provided strong evidence that the $5HT_{2c}$ receptor is primarily responsible for mediating the inhibition of feeding observed with fenfluramine treatment. It was observed that the anorexigenic efficacy of fenflouramine was greatly attenuated in these $5HT_{2c}$ null animals[21]. Interestingly, phenotypic characterization of these mice lacking the $5HT_{2c}$ receptor revealed that they are hyperphagic and develop adult onset obesity[22]. More recently, electrophysiological and molecular techniques have allowed for a more precise characterization of the $5HT_{2c}$ receptor's role in feeding. Heisler et al provide strong evidence that pro-opiomelanocortin (POMC) neurons located within the arcuate nucleus of the

hypothalamus express the $5HT_{2c}$ receptor and that receptor activation promotes excitability and α-MSH release[23]. Accumulating evidence implicating the $5HT_{2c}$ receptor as a key component in the regulation of feeding behavior has made the receptor an attractive target for development of anti-obesity drugs[20].

To understand the $5HT_{2c}$ receptor's role in physiology and attempt to develop informed pharmacologic interventions it is imperative to consider the variable signaling properties observed among different receptor isoforms. RNA editing of transcripts encoding $5HT_{2c}$ receptor results in production of receptor proteins with profound differences in constitutive activity and 5HT mediated signaling efficacy. Several labs have generated mice genetically modified to express only protein isoforms resulting from fully edited transcripts (VGV) or non-edited transcripts (INI) to study the effects of these isoforms respectively *in vivo*. Significant metabolic alterations in the animals which only express the VGV receptor isoform suggest that the role of this receptor in regulating metabolism is more complicated that previously appreciated. Specifically, these mice display increased basal metabolic rate which was found to be independent of the melanocortin- 4 receptor. Consistent with the hypothesis that efficient excitatory drive onto POMC neurons by the $5HT_{2c}$ receptor is required for normal inhibition of feeding, these mice display adult onset hyperphagia similar to that observed in the $5HT_{2c}$ null animals[24]. Currently, it is not clear if this hyperphagia is directly related deficient activation POMC neurons in the Arc, or an indirect feedback mechanism related the enhanced basal metabolic rate. Importantly, these results demonstrate a previously unappreciated fundamental role for the $5HT_{2c}$ receptor in regulating metabolic function.

Throughout evolution, animals have had to cope with tremendous variations in food availability, across seasons and through generations, requiring the evolution of highly dynamic metabolic regulation. Serotonin plays an important role in maintaining many aspects of homeostasis, but the specific role that RNA editing plays in these processes is not known. Interestingly, it has been observed that prenatal dietary deficiencies can lead to altered brain serotonin homeostasis[25], metabolic disfunction, and reduced sensitivity to d-fenflouramine[26]. Specifically, Lopez de Souza et al observed significant reductions in d-fenfluramine-induced suppression of feeding and arcuate c-fos activation in rats exposed to perinatal protein deficiency. The levels of $5HT_{2c}$ receptor transcripts are unchanged in these animals suggesting that a mechanism downstream of receptor expression is responsible for this lack of sensitivity[26]. The RNA-editing profile for the $5HT_{2c}$ receptor has not been characterized in these rats, but alterations in editing have the potential to contribute to the findings observed in these studies. Characterization of RNA-editing dynamics in POMC neurons during normal development and in response to prenatal malnutrition may elucidate the relationship between metabolic disfunction and $5HT_{2c}$ receptor function.

$5HT_{2C}$ RECEPTORS REGULATE MESOLIMBIC DOPAMINE SIGNALING

Animals possess the unique ability to physically interact with their environment in order to promote their own survival and reproduction. Goal directed behavior and adaptive learning have evolved in higher vertebrates to facilitate this need to efficiently respond to the nearly infinite possible circumstances an animal may find itself in. Mechanistically, goal directed behavior and adaptive learning requires; goal identification, perception of relevant sensory stimuli, generation of possible motor sequences, and anticipation of the relative utility of particular motor sequences in attaining the goal. Furthermore, the ability to encode reward upon the execution of effective motor sequences allows animals to modify and perfect behavioral sequences to efficiently achieve goals. The mesolimbic system, which includes; the Nucleus Accumbens (NAc), olfactory tubercle, ventral pallidum (VP), mediodorsal thalamus, ventral tegmental area, lateral hypothalamus, limbic cortex, and amygdala provides the neural substrate for reward associated learning and motivated behavior[27]. Dopamine (DA) release in the NAc and olfactory tubercle is thought to be a key component in goal directed selection of motor programs and underlie the neural coding of reward[28]. Dopamine is supplied to the ventral striatum primarily by groups of neurons located in the midbrain known collectively as the ventral tegmental area (VTA), and its release in the medial shell of the NAc and medial olfactory tubercle directly correlates with the rewarding effects of achieving goals as well as the reinforcing effects of drugs of abuse[28].

5HT is supplied to the structures of the mesolimbic system by neurons in the dorsal raphe and plays a significant role in the regulation of NAc DA release[33] and $5HT_{2c}$ receptor transcripts can be detected by in situ hybridization the VTA and throughout the NAc[17]. Studies in which selective $5HT_{2c}$ receptor agonists, antagonists, and inverse agonists are administered while monitoring DA levels in NAc via microdialysis suggest that activation of $5HT_{2c}$ receptors have a net inhibitory effect on both baseline and drug induced DA release in the ventral striatum. Navailles et al showed that intra-accumbal infusion of inverse agonist SB 206553, but not antagonist SB 242084, increased basal DA efflux in the NAc. They also showed that the acute decrease in

basal accumbal DA levels elicited by systemic infusion of agonist Ro 60-0175 was attenuated by intra VTA infusion of antagonist SB 242084[39]. Taken together, these results suggest that phasic activation of receptors in the VTA attenuates DA release and constitutive activity of receptors in the NAc provide tonic suppression of DA release. Further supporting an inhibitory role for $5HT_{2c}$ receptors with respect to DA release, Gobert et al showed that systemic administration of inverse agonist and agonist dose dependently increased and decreased respectively, the firing rate of DAergic neurons in the VTA[33]. Activation of $5HT_{2c}$ receptors has been shown to excite cells via activation of PLC and subsequent modulation of ion channel activity[29,30]. These observations have lead to the hypothesis that $5HT_{2c}$ receptors in the NAc and VTA negatively regulate DA release by DAergic neurons by activating inhibitory GABAergic interneurons which, in turn, directly inhibit DAergic neuron activity. In agreement with this hypothesis, immunoreactivity has been observed primarily in GABAergic cell bodies in the VTA and NAc as implied by co-staining of cells with antibodies against glutamate decarboxylase the enzyme that synthesizes GABA from glutamate[31, 32].

Recently, several studies have attempted to evaluate the effects of various serotonin receptor ligands on the acquisition of stimulant addiction and on reinstatement of drug seeking behavior after extinction. The inhibitory role of $5HT_{2c}$ receptor agonists on DA release has lead to the hypothesis that such drugs could be effective in treating addiction. Indeed, several studies have indicated that systemic administration of agonists decreases the acute hyperlocamotive response to stimulants and reduces self-administration and reinstatement of cocaine seeking bahavior[34]. As noted above, investigation into the regulation of DA by $5HT_{2c}$ receptors has indicated that several distinct populations of receptors exist each with different functional roles in regulation of DA[19, 34]. All of the subcortical $5HT_{2c}$ receptor populations analyzed to date seem to provide a net inhibitory drive on NAc DA release, but the differential responses to inverse agonists, antagonists, and agonists suggests that the receptors play distinct roles in responding to 5HT. Functional differences of 5HT populations merit further investigation; it is possible that select cell types express different edited isoforms with variable levels of constitutive activity and provide tonic or phasic control of DA release respectively.

CONCLUSIONS

A number of studies have attempted to profile the distribution of $5HT_{2c}$ receptor edited isofoms in the brains regions of humans who had suffered from neuro-pathologies, particularly depression and schizophrenia[35,36]. One study by Gurevich et al reported that changes in editing observed in pre-frontal cortex of suicide victims was the opposite (at each respective editing site) of the changes that could be induced by treating mice with the SSRI fluoxetine[36]. The authors suggested not only that altered editing may contribute to pathology in humans, but also that editing could be manipulated by pharmacologic intervention affecting 5HT tone. Following these findings, effort was spent attempting to elucidate how sustained alterations in 5HT tone via pharmacologic intervention might affect editing of $5HT_{2c}$ receptor transcripts. Englander and Gurevich subsequently provided evidence for dynamic modulation of RNA editing by a number of factors including stress[37], 5HT depletion[38], and SSRI treatment[36,37]. The possibility that RNA editing can be dynamically modulated in a substrate specific manner carries compelling implications with respect to normal and pathologic brain function. While the relationship between RNA editing dynamics, drug treatment, and behavioral pathology is not understood, it is an important phenomenon to consider when studying CNS function.

Accumulating evidence implies that the $5HT_{2c}$ receptor is a key component in the transduction of 5HT's signal in the CNS. This review discussed receptor function in two key systems which regulate fundamental aspects of behavior; hypothalamic regulation of metabolism, and DA regulation in the ventral striatum. In addition to being medically relevant behavioral systems, these circuits are relatively well characterized, have readily observable outputs, and several well established experimental paradigms. With the recent development of tools such as knock-in mice expressing only specific edited isoforms of the receptor, and selective ligands, it will be possible to begin understanding the role of this neurotransmitter receptor's unique and complex molecular biology. Serotonin related drug intervention is at the forefront of the struggle to treat a wide array of psychiatric disorders. To develop informed therapies based on modulation of serotonin signaling it is imperative to understand the role played by this prominent monoamine receptor.

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    This study provides evidence for the roles of different populations of receptors in distinct brain regions regulating NAc dopamine release.

FURTHER INFORMATION

Ron Emeson's Lab:
http://kc.vanderbilt.edu/site/people/1450/emeson-ron.aspx