



Trip Report for
“Serotonin Club Meeting,”
Keble College, Oxford, England, July 17-20, 2008

David D. Manning, Ph. D.

August 21, 2008

Abstract: The Serotonin Club meeting was held at Keble College, Oxford, England from July 17-20, 2008. The Serotonin Club is an association of scientists from around the globe with a common interest in the study of the neurotransmitter serotonin. This year's club meeting held in Oxford was an official satellite meeting to The Federation of European Pharmacological Societies Congress (EPHAR) held in Manchester. The meeting had several hundred attendees. Presentation topics were broad and included basic science, pharmacology and clinical findings. The text that follows summarizes selected topics of personal interest from the meeting.

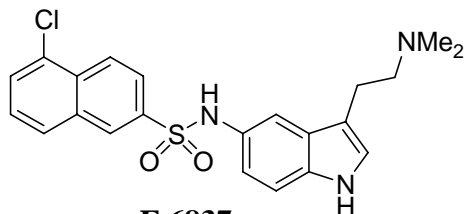
Serotonin and Emotional Processing

Catherine Harmer, (University of Oxford), UK.

Early predictors that can help select appropriate drug treatment for depression patients are highly sought. The study of antidepressants on emotional processing may lead to an early predictor of drug efficacy. Various models which measure emotional processing suggest that antidepressant drugs increase the processing of positive versus negative emotional information. For example, changes in positive emotional processing were apparent early with antidepressant treatment, even with acute administration in human subjects. These findings have led to the hypothesis that the therapeutic improvements in mood and associated symptoms of drug-treated depressed patients are downstream of early changes in emotional processing and that the common delay seen in mood improvements are due to patient adaptation to new emotional input. In agreement with this notion, the research group found that early shifts in emotional bias were followed by improvements in therapeutic response to antidepressant treatment after a six week period. In another study, the NK1 antagonist aprepitant failed to affect emotional processing in healthy patients to the same degree as routine antidepressant treatment which is consistent with its poor performance in the treatment of depression. The findings presented support that the idea that measures of emotional processing may be useful as an early predictor of antidepressant efficacy.

Serotonergic Strategies to Prevent Antipsychotic Induced Weight Gain

A. Fisas¹, X. Codony¹, JM Vela¹, S. Cheetham², H. Jackson², D. Heal², H. Buschmann¹,
¹Laboratories Esteve, Spain; ²Renasci Consultancy Ltd. UK.



E 6837

5-HT₆ K_i = 0.74 nM

One of the few structures displayed was E6837, described as a 5-HT₆ receptor agonist (Esteve Laboratories). The researchers presented findings from a study aimed at demonstrating whether E6837 could prevent or reduce weight gain in olanzepine-induced obese rats. The goal was to support the notion that a combination therapy of a 5-HT₆ receptor ligand and an atypical antipsychotic could lead to an improved schizophrenia treatment. The findings presented for E6837 indicated that it not only prevented weight gain (olanzepine treated animals +5.6% vs. vehicle, 14 day study) but also showed a weight loss (-6.6% vs. vehicle) in animals treated with both olanzepine and E6837. Alone E6837 produced a weight loss of -7.2% vs. vehicle. The gain in weight in the olanzepine group was attributed to increased food intake whereas the loss in weight for E6837 was largely attributed to decreases in food intake. Notable was that the dose of olanzepine was rather modest (3 mpk bid) compared to therapeutic doses and to that of E6837 (30 mpk bid). Ancillary comments during the question period asserted that the compound increased memory functions however the cognition models were not presented. The cognition models were apparently not done in the presence of olanzepine.

Serotonin and GI clinical Disorders

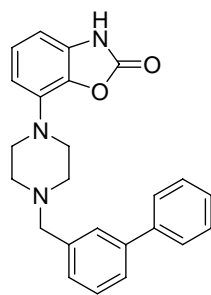
Robin Spiller, (University of Nottingham), UK.

Dr Spiller gave a clinicians view of serotonin and GI disorders. The enterochromaffin cells (EC) are the “taste receptors” of the gut. In response to stimuli such as toxins or pressure (i.e. from luminal content), the neurotransmitter serotonin is released from storage vesicles within these cells. The release of serotonin can activate receptors on primary afferent neurons within the mucosa which modulate secretion and GI motility. Serotonin’s action is checked by the action of the serotonin reuptake transporter (SERT) which clears excess serotonin. Several maladies have been strongly linked to increase serotonin release including nausea and vomiting from chemotherapy, carcinoid syndrome and irritable bowel syndrome. Parasitic infections of the GI tract also are thought to lead to increased levels of mucosal 5-HT and is an emerging theory as one cause of IBS. Further supporting the role of serotonin in IBS, decreased SERT levels have been

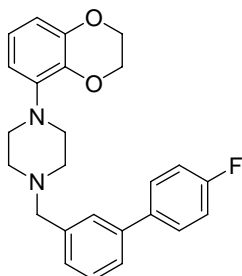
observed in animal models of GI infection and inflammation. 5-HT₃ receptor antagonists are well known to inhibit the effects of chemotherapy induced nausea and vomiting presumably via block of the increased serotonin signal from the damaged EC cells. The 5-HT₃ receptor antagonist alosetron has been used to treat IBS-D although apparent associated severe ischemic colitis has limited its use. Ramosetron was pointed to as a potential second generation 5-HT₃ receptor antagonist. Ramosetron was approved in Japan for IBS-D shortly after the meeting. Whether this agent will suffer the same fate as alosetron is unclear. During question period it was noted that ischemic colitis was also reported for tegaserod, a 5-HT₄ receptor agonist and suggested that ischemia might be a general response to perturbing the 5-HT system. Dr. Spiller however was not convinced that the reports of ischemic colitis with tegaserod were confirmed. The cause of ischemic colitis is simply not understood.

Potential Role for 5-HT_{1A} Receptor Agonism in Ameliorating Negative and Cognitive Symptoms in Schizophrenia.

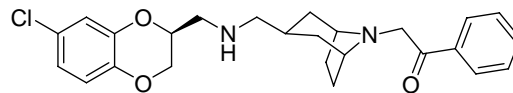
D. Heal¹, J. Arnt², M. Pausch³, A. McCreary⁴, J. Neill⁵ ¹*RenaSci Consultancy, BioCity Nottingham, UK;* ²*Research, H. Lundbeck, Denmark;* ³*Discovery Neuroscience, Wyeth Research, Princeton NJ, USA;* ⁴*Solvay Pharmaceuticals Research, Netherlands;* ⁵*School of Pharmacy, University of Bradford, Bradford, UK.*



Bifeprunox
Preregistraion
Schizophrenia



SLV-313
Phase II Schizophrenia



SSR 181507
Phase I Schizophrenia

Second generation antipsychotics the so called “atypicals” have improved schizophrenia treatment by reducing extrapyramidal symptoms and tardive dyskinesia that result from treatment with the typical antipsychotics. These successes have been attributed to enhancing 5-HT_{2A} receptor antagonist properties into the newer compounds. Despite the advances observed for these medicants, limitations remain for treating negative symptoms and cognitive deficits commonly seen in schizophrenic patients. Besides 5-HT_{2A}, other serotonin receptors have been investigated for potential to improve efficacy in schizophrenia. In this presentation, a case was made that augmentation of the 5-HT_{1A} receptor component (i.e. agonist or partial agonist) of an antipsychotic drug has potential to treat certain aspects of both cognitive deficit and negative symptoms. Several comparative results from preclinical pharmacology studies of bifeprunox (D₂ partial agonist, 5-HT_{1A} partial agonist), SSR 181607 (D₂ partial agonist, 5-HT_{1A} partial agonist) and SLV 313 (D₂ antagonist, 5-HT_{1A} full agonist) were presented. Briefly summarizing

the preclinical findings: (1) bifeprunox and SLV 313 suppressed ultrasonic vocalizations (a measure of anxiolytic activity); (2) SLV 313 and bifeprunox exhibited activity in a stress induced hypothermia model; (3) SLV 313 dose dependently reversed hyperactivity induced by chronic administration of antidepressants in an olfactory bulbectomized rodent model; (4) Neither bifeprunox nor SLV 313 reversed PCP-induced social withdrawal whereas SSR 181507 did show some effect; (5) bifeprunox and SLV 313 reversed MK-801 deficits in a novel object recognition model (memory test). The above findings supported the concept that increased 5-HT_{1A} receptor activity could lead to improvements cognitive deficits and negative symptoms in humans. A lively discussion followed this presentation.

AMR-SER-67: A Novel and Selective High Affinity 5-HT₃ Receptor Partial Agonist

Alexander Usyatinsky¹, Christopher L. Cioffi¹, Svetlana Dobritsa⁴, Kevin Fitzpatrick¹, William G. Earley², Amy S. Butler⁶, Catherine A. Brady⁶, Nicholas M. Barnes⁶, Marlene L. Cohen⁵ and David D. Manning¹ ¹*Discovery R&D Chemistry*, ²*Medicinal Chemistry*, and ³*Metabolism and Biotransformations*, AMRI, Albany, NY; ⁴*Discovery R&D In Vitro Biology*, AMRI Bothell Research Center, Bothell, WA; ⁵*Creative Pharmacology Solutions LLC*, Carmel, IN; ⁶*Celentyx Ltd*, Edgbaston, Birmingham, UK.

Irritable bowel syndrome (IBS) is a painful, debilitating functional disorder of the bowel that decreases quality of life. The 5-HT₃ receptor antagonist alosetron has been used therapeutically, although ischemic bowel injury has been problematic for this compound. Partial activation of the 5-HT₃ receptor is an emerging strategy for the potential treatment of IBS in an effort to mitigate the potential complication of ischemia. Compounds with high 5-HT₃ receptor affinity and low intrinsic functional activity may be superior to current options for the treatment of diarrhea predominant IBS (IBS-D). The aim of the AMRI research team was to identify a new class of selective 5-HT₃ receptor ligands with weak partial agonist activity. Compounds were tested for their ability to evoke 5-HT₃ receptor mediated responses (\pm the presence of the positive allosteric modulator, 5-chloroindole that potentiates preferentially the intrinsic activity of partial agonists) in human embryonic kidney (HEK293) cells expressing the *h5-HT_{3A}* receptor subunit. [Ca²⁺]_i was used as the functional readout. In the present study, all agonist- and partial agonist-induced responses were antagonized by the selective 5-HT₃ receptor antagonists, ondansetron (500 nM) and granisetron (100 nM). AMR-SER-67 (EC₅₀ = 12.6 \pm 6.1 nM) exhibited an E_{max} value of 6 \pm 2 % relative to the maximum 5-HT response. The E_{max} increased to 23 \pm 2 % in the presence of 5-chloroindole (10 μ M). Alosetron failed to induce a response with or without 5-chloroindole, consistent with it being a 5-HT₃ antagonist. Additionally, AMR-SER-67 did not show significant affinity for over 65 off-target receptors and ten serotonin receptor subtypes. AMR-SER-67 exemplifies this novel chemical series, possessing high affinity (*h5-HT₃* K_i = 1.2 nM) and weak 5-HT₃ receptor partial agonist activity. The AMRI work was presented as a poster at the meeting.