November 2008

Kopf Carrier #67

KOPF CARRIER

PUBLISHED BY DAVID KOPF INSTRUMENTS ■ TUJUNGA, CALIFORNIA

Anesthetizing the Blues

German Torres[a], Brian H. Hallas[a], Judith M. Horowitz[b]

[a]Department of Neuroscience, New York College of Osteopathic Medicine of New York Institute of Technology, Old Westbury, NY 11568, USA • [b]Department of Psychology, Clinical Neuroscience Laboratory, Medaille College, Buffalo, NY 14214, USA

***Corresponding Author:**
German Torres, Ph.D.
Associate Professor
Department of Neuroscience,
NYCOM/NYIT
PO Box 8000
Old Westbury, NY 11568 USA
Telephone: 516-686-3806
Fax: 516-686-3750
E-mail: torresg@nyit.edu

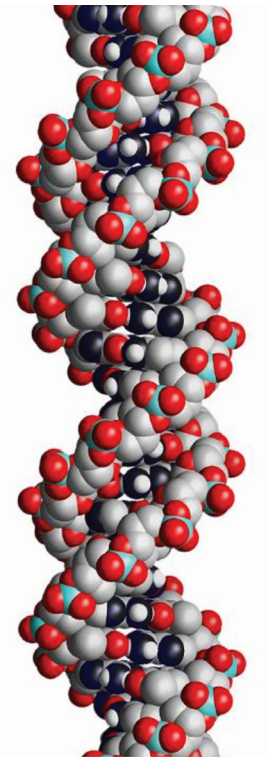
Major depression is a chronic, recurrent mood disorder that causes significant disability and disease burden throughout the world. Not surprisingly, there is an enormous demand for (a) finding appropriate medications and devices for treating the clinical symptoms and (b) identifying the underlying molecular mechanisms of the disease. Currently, most therapeutic treatments of depression indirectly target the serotonin (5-HT) and norepinephrine (NE) systems of the brain, as these neurotransmitters have long been considered promising and mechanistically relevant to the etiology of mood disorders (Manji et al., 2001; Belmaker and Agam, 2008). However, selective 5-HT reuptake inhibitors such as sertraline, fluoxetine and paroxetine do not always substantially improve clinical outcome, and when they do show efficacy, it takes weeks of treatment to achieve an appreciable clinical effect. These observations suggest that a 5-HT and NE hypothesis of major depression is incomplete at best, and that novel, rapid onset therapeutic options for depression must be considered (Box 1).

This essay describes one new pharmacological treatment (ketamine) for chronic melancholia and behavioral despair which targets a particular set of glutamate (GLU) receptors (Leheste et al., 2008). The fact that a pediatric anesthetic produces a relatively sustained and rapid antidepressant effect in patients with major depression, suggests the possibility that anesthetic derivatives of ketamine may be used as novel treatments for mood disorders.

Glutamate is the brain's most pervasive neurotransmitter as it is heavily involved in almost all excitatory or "go" signaling events between nerve cells that are attuned to it (Moghaddam, 2003). Accordingly, virtually all

Box 1. Multiple somatic interventions reflect the complexity of major depression. Aside from pharmacological intervention, there are several devices currently used to treat patients with difficult to treat chronic or recurrent depression. These devices include electroconvulsive therapy (ECT), vagus nerve stimulation (VNS) and most recently, transcranial magnetic stimulation (TMS). Repeated administration of ECT is one of the most effective treatments of depression, particularly in suicidality situations when clinical intervention is immediately required. There is no conclusive regional specificity of ECT effects. The vagus nerve (cranial nerve 10) has afferent fibers that lead up toward the brain, including indirect input to the locus coeruleus, a major site of NE synthesis whose neurons make synaptic connections with the amygdala and orbito-frontal cortex. Vagus nerve stimulation appears to provide both acute symptom relief and continued benefits in patients with treatment resistance depression (George et al., 2000). Transcranial magnetic stimulation therapy is a relatively new approach for treating melancholia and overall behavioral despair. However, its antidepressant mechanisms of action are not well understood. As in ECT, there is no conclusive regional specificity of TMS effects although there is evidence that left prefrontal cortex application of rapid-rate TMS improves depression scores in melancholic patients (Chang, 2004). The reversible and adjustable nature of the above therapies is an appealing, if rather coarse, approach to treating depression. Large-scale clinical trials are now under way to test the possibility of using deep brain stimulation (e.g., in the sub-callosal cingulate gyrus) for the treatment of major depression. Deep brain stimulation is delivered *via* deeply implanted electrodes to alter abnormal chemical circuits underlying mood disorders.

nerve cells contain receptors that allow them to respond to GLU (Edwards, 2007). Glutamate synapses are therefore well positioned to relay messages between neurons and to link neurological processes at the cellular level to cognitive processes observed at the behavioral level. Glutamate exerts all of its synaptic actions through trans-membrane-bound receptors that act directly as ion channels and receptors that signal through G proteins and cyclic mononucleotides. One of these receptors is the so-called N-Methyl-D-Aspartate (NMDA) receptor (Haines, 2002). Within the NMDA receptor, at relatively hydrophobic regions of the trans-membrane site of the channel, there are binding sites for ketamine and phencyclidine (PCP). Both ketamine and PCP are dissociative (detached from surrounding) anesthetics capable of inducing analgesia, psychomimetic behavior and a catatonic state of unconsciousness (Moghaddam and Adams, 1998). Ketamine inhibits NMDA re-

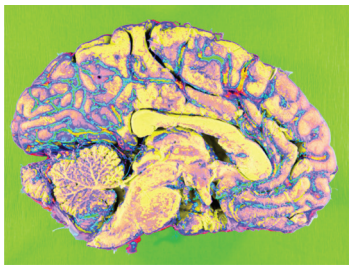


Box 2. Genes are arguably the strongest contenders for involvement in major depression. It is generally thought that "risk" genes can predispose someone to a range of psychiatric conditions (e.g., apathy) if he or she encounters a stressful life crisis (e.g., a relationship gone awry). Thus, major depression is assumed to have a gene-environment interaction. However, only a tiny list of candidate genes has been found to be linked with the disease. Further, there is no clear understanding as to how a stressful environment can trigger a depressive episode. For example, how does a neuron interpret the presence of a stressful event or anxiety overload and start transmitting signals that trigger a life crisis? Does the signaling in stress response stem from a common neural mechanism or from different mechanisms that subsequently become integrated in the prefrontal cortex? In addition, although symptoms are the best indicators of the disease, poor and inconsistent diagnoses often fail separating clinical symptoms with distinct underlying genetics. This likely explains why large-scale clinical trials show remission rates of approximately 30%, which are clearly less that optimal in psychiatry. Image obtained from NIGMS (National Institute of General Medical Sciences) Image Gallery and featured in Genes Fact Sheet. Content created November 2006.

ceptor function (and to a lesser degree mu and kappa opioid receptors as well), yet there is little evidence that this drug affects $GABA_A$ receptors, the primary targets of most anesthetics. Although ketamine induces transient psychedelic hallucinations, it also appears to relieve the burden of major depression by an unknown mechanism (Box 2).

For instance, intravenous (IV) treatment with ketamine at a non-anesthetic dose of 0.5 mg/kg results in a rapid and sustainable amelioration of depression symptoms as discerned by means of clinical interviews, the 21-item Hamilton Depression Rating Scale and the 21-item Beck Depression Inventory (Zarate et al., 2006; Liebrenz et al., 2007; Maeng et al., 2007). The fact that ketamine is administered IV may in part be responsible for its rapid onset of action in the brain (within 2 hr) and also by the fact that IV administration bypasses the first-pass metabolism process. This would certainly enhance the amount of ketamine that reaches brain sites suspected in the pathology of major depression.

Regardless, ketamine exerts a rapid therapeutic response in a refractory population of depressed patients (Berman et al., 2000; Amiel and Mathew, 2007). This finding provides a convincing association between NMDA receptor function and depression, and suggests that a deficit in key proteins of the GLU system is linked to mood disorders. In this regard, several clinical studies have previously suggested associations between dysfunction of the GLU system and disabling clinical conditions characterized by overwhelming despair, including unipolar major depression. For instance, levels of GLU are elevated in the occipital cortex of depressed patients when compared with sex-matched controls (Sanacora et al., 2007; Hashimoto et al., 2007). Further, anticonvulsant drugs that inhibit GLU release such as lamotrigine and riluzole are effective in treating bouts of depression (Sanacora et al., 2004; Du et al., 2007; Box 3). Together, these data represent compelling evidence that GLU and its receptors have a pivotal role in both the cause of major depression and perhaps its successful treatment. Aside from the need to further



Box 3. Brain structures thought to be relevant for the pathogenesis of major depression. Regardless of the putative genes in question and the environmental cues that signal the presence of stress, major depression and dysthymic disorders are considered to be diseases of an ailing brain. In this regard, several brain areas and nerve circuits have been identified to be involved in emotions that are affected by current anxiety and depression drugs. These brain sites include the prefrontal cortex and the amygdala, brain regions that evaluate threats in the environment and then coordinate appropriate behavioral responses to avoid or mitigate them, and the hippocampus, a region involved in making factual memories. It is thought that dysfunction in these brain areas and their interconnected synapses likely yield qualitative changes in the subjective experience of stress and/or fear. Thus, a decidedly different brain circuit, which is modified both by the initial genetic perturbation and a social insult, is established in a pathogenic trajectory of melancholia and psychological despair. Learning more about genes and environmental interactions that regulate mood phenomena would point to new biochemical pathways at which to direct treatment.

replicate the above studies, more studies are also needed to determine whether the effects of ketamine on the cortex, the amygdala and/or the hippocampus are merely correlative or whether there is a causal relationship between ketamine administration and cognitive improvement in patients. In this regard, anesthetic and/or analgesic effects of ketamine must be ruled out, as one can argue that the therapeutic properties of ketamine might include some type of “numbness” of the ailing brain. Along the same lines, it is also conceivable that ketamine might induce a mild form of psychosis in depressed individuals which may account for the improvement of their mood. The stakes in this clarification are high for both mental-health professionals and patients.

Acknowledgments

This work was supported in part by an NIH grant (#R15MH645-01A1) to JMH and GT. We thank Elizabeth A. Doran (NYCOM Academic Technologies Group), Pat Jacovina and Judith M. Cisek (Department of Neuroscience) for their excellent technical assistance.

Biographies of the Authors

Dr. German Torres (torresg@nyit.edu) received a Ph.D. in Neuroscience from the University of California at Santa Barbara and is currently an Associate Professor in the Department of Neuroscience and Histology at the New York College of Medicine of New York Institute of Technology. His specific research interests are centered on the biological basis of mental disorders. Dr. German Torres is supported by grants from the National Institutes of Health and The Johns Hopkins University.

Contact Information: New York College of Osteopathic Medicine of New York Institute of Technology, Northern Blvd., Old Westbury, NY 11568 (516) 686-3806.

Dr. Brian Hallas (bhallas@nyit.edu) received his Ph.D. in neurobiology from Purdue University in 1979. He also holds an M.S. in biology from Purdue University, a B.A. in Psychology, and a B.S. in Biology from University of Hartford. He has been awarded numerous research grants and has authored many articles in scientific journals. He is the recipient of various honors and awards, most recently the prestigious Presidential Service Award from New York Institute of Technology

in 2007. In 2004, he was awarded a fellowship by the Heritage Foundation Health Policy for Research in Health Policy based on stem cell research. From 2003 to 2007, he was Associate Dean of Research at the New York College of Osteopathic Medicine of New York Institute of Technology, where he is currently Chair and Professor of the Department of Neuroscience. He has published over 70 peer reviewed articles, several book chapters and 225 abstracts.

Dr. Judith Horowitz (jhorowitz@medaille.edu) received a Ph.D. in biopsychology from the State University of New York at Buffalo, and has continued studying the relationship between brain and behavior. She has published over two dozen articles in the areas of depression, Parkinson's Disease, schizophrenia, and drug addiction. She has received extramural funding from the National Institutes of Health and the National Institute of Mental Health, the National Association for Research on Schizophrenia and Depression, and the Parkinson's Foundation. She has taught in Medaille's Psychology Program since 1997, and now serves the College as the Dean of the School of Adult and Graduate Education (SAGE).

References

Amiel, J.M.; Mathew, S.J. *Curr. Psychiatry Rep.*, 2007, 9(4), 278-293.

Belmaker, R.H.; Agam, G. *N. Engl. J. Med*, 2008, 358, 55-68.

Berman, R.M.; Cappiello, A.; Anand, A.; Oren, D.A.; Heninger, G.R.; Charney, D.S.; Krystal, J.H. *Biol. Psychiatry*, 2000, 47(4), 351-354.

Chang, J.Y. J. *of Pharm.*, 2004, 309, 1-7.

Du, J.; Suzuki, K.; Wei, Y.; Wang, Y.; Blumenthal, R.; Chen, Z.; Falke, C.; Zarate, C.A.; Manji, H.K. *Neuropsychopharmacology*, 2007, 32(4), 793-802.

Edwards, R. H. *Neuron*, 2007, 55, 835-850.

George, M.S.; Sackeim, H.A.; Rush, A,J.; Marangell, L.B.; Nahas, Z.; Husian, M.M.; Lisanby, S.; Burt, T.; Goldman, J.; Ballenger, J.C. *Biol. Psychiatry*, 2000, 47, 287-295.

Haines, D.E. *Fundamental Neuroscience*, Churchhill Livingstone: Pennsylvania, 2002.

Hashimoto, K.; Sawa A.; Iyo, M. *Biol. Psychiatry*, 2007, 62(11), 1310-1316.

Leheste, J.R.; Curcio, C.; Baldinger, L.; Sarwar, S.; Zakhary, S.M.; Hallas, B. H.; Horowitz, J.M.; Torres, G. *Central Nervous System Agents in Medicinal Chemistry*, 2008 (In Press).

Liebrenz, M.; Borgeat, A.; Leisinger, R.; Stohler, R. *Swiss Med. Wkly.*, 2007, 137, 234-236.

Maeng, S.; Zarate, C.A. Curr. *Psychiatry Rep*, 2007, 9(6), 467-74.

Manji, H. K.; Drevets, W. C.; Charney, D. S. *Nature Med.*, 2001, 7, 541-547.

Moghaddam, B. *Neuron*, 2003, 40, 881-884.

Moghaddam, B.; Adams, B. *Science*, 1998, 281, 1349-1351.

Sanacora, G.; Gueorguieva, R.; Epperson, C.N.; Wu, Y.T.; Appel M.; Rothman, D.L.; Krystal, J.H.; Mason, G.F. *Arch. Gen. Psychiatry*, 2004, 61(7), 705-713.

Sanacora, G.; Kendell, S.F.; Levin, Y.; Simen, A.A.; Fenton, L.R.; Coric, V.; Krystal, *J.H. Biol. Psychiatry*, 2007, 61(6), 822-825.

Zarate, C.A.; Singh, J. B.; Carlson, P.J.; Brutsche, N.E.; Ameli, R.; Luckenbaugh, M.A.; Charney, D.S.; Manui, H. K. *Arch. Gen. Psychiatry*, 2006, 63, 856-857.

Editor's Column

It is time for many of us to prepare for the big event of the year in the world of neuroscience; the annual Society for Neuroscience meetings, this year in Washington DC. I remember attending the very first meeting of the society in 1971, also in Washington DC. It was much smaller than this meeting will be, as there were about 1,396 in attendance. It was the right time for the new society, and the membership grew very rapidly. This year, there will probably be close to 34,000 in attendance. I do hope you are planning to attend.

While you are at the meeting, please stop by the David Kopf Instruments booth (1323) and say hello to the great people who make such wonderful stereotaxic instruments and associated equipment for the neuroscience community. As most of you know, Kopf Instruments is the oldest and best full line of stereotaxic and related equipment in the world. The company has supported the neuroscience community since its inception in 1956. Kopf Instruments was one of the first major supporters of the Society for Neuroscience and has helped several other organizations in the neuroscience community over the years.

In 2005, in memory of David Kopf who founded David Kopf Instruments and passed away in 2004, the company sponsored the David Kopf Lecture on Neuroethics, now an annual lecture at the Society for Neuroscience meeting. This year's speaker is Patricia S. Churchland, B.Phil from the University of California, San Diego. She will speak on "How Do Brains Navigate Their Social/Moral World." The lecture will be on Monday, November 17 from 10-11 am. We invite all to come to this intriguing lecture. We are very pleased that the Society for Neuroscience has chosen Particia Churchland as this year's honored speaker.

We of the Kopf family, look forward to seeing you in Washington where you can see many of the new and improved instruments in the Kopf Instrument line.

This issue, number 67 of the *Carrier*, was written by German Torres, Brian H. Hallas and Judith M. Horowitz from the College of Osteopathic Medicine at the New York Institute of Technology and Medaille College in Buffalo, NY. Brian and his colleagues have written several *Carrier* articles and this one is another in a fine series of contributions from them. They describe the potentially beneficial effects of ketamine in the treatment of clinical depression. It is an interesting article for all in the neuroscience community, whether you work in the area of mental illness or not.

Here in Florida, we are almost at the end of the hurricane season and have not had a major storm in our area of south Florida. However, we will shut the hurricane shutters on our home when we travel to Washingon DC just in case something were to develop. The hurricane season begins at the first of June and ends at on November 30, but the peak month is September with another smaller peak in October. So we should be home free this year. It is interesting to note that during the first half of the season hurricanes usually form off Africa and progress across the Atlantic Ocean, giving plenty of time to prepare, although the track is often erratic. At this time of year, most hurricanes form in the Caribbean area and progress north, giving a much shorter time for preparation. So, we will be prepared just in case.

If you want contribute an article for the *Carrier*, please contact me or send a message to David Kopf Instruments. All back issues of the *Carrier* are available for download on the company website (kopfinstruments.com) so you can look at what has been published there. The company supplies a $500 honorarium for each article published. We would be pleased to send you the instructions for *Carrier* authors if you need them.

Michael M. Patterson, Ph.D.
Science Editor
David Kopf Instruments
954-288-5518
954-452-6812 (FAX)
drmikep@earthlink.net