EDITORIAL

“Glutamatergic-based Rapid Acting Antidepressants: The Link to Synaptic Plasticity”

Since the emergence of Miltown in the 1950's, through the development of popular drugs such as Librium and Valium, and presently with the SSRIs best exemplified by Prozac, antidepressants have been viable therapies for many with mood disorders and especially depression. Moreover, since World War II, there has been a virtual explosion in the prescription and use of such drugs. Unfortunately, no antidepressant has ever been effective for more than 50% of those diagnosed-usually the percentage is markedly lower than that, the drugs often take several weeks at least to show any signs of efficacy and long-term use inevitably leads to difficult to manage side effects. Clearly, there remains a great unmet need for truly effective antidepressant treatment.

Recently, a body of basic and clinical research has emerged that strongly suggests that glutamatergic-driven synaptic plasticity-predominantly modulated by NMDA receptor triggered AMPA receptor modulation-could be a new frontier in psychiatry.

The idea that alterations in synaptic plasticity associated with normal brain development and function are associated with depression, etc. is very compelling as the molecular mechanisms underlying learning and memory have been studied in great detail over the years. Glutamate concentrations in the brain are higher than any other neurotransmitter. And clinical trial data with D-cycloserine, an NMDA receptor glycine site partial agonist, ketamine, a putative NMDA receptor antagonist and Rapastinel, an NMDA specific receptor modulator with partial agonist properties have all shown significant effects. Moreover, in the case of ketamine and Rapastinel clinical data have been reportedly shown both rapid acting and long lasting antidepressant effects. D-cycloserine appears to have marked potential in schizophrenia.

Thus, this collection of reviews was compiled to address the current state of the field of “Glutamatergic-based rapid acting antidepressants: The link to synaptic plasticity”. This collection combines manuscripts that address various aspects of the mechanistic underpinnings of how clinically active compounds like D-cycloserine, ketamine and Rapastinel work to alleviate symptoms of depression and schizophrenia combined with key papers from research groups that have conducted the clinical trials. Together, these reviews give a state-of-the-art look at the entire field; where it started, where it is going, and the strengths and weaknesses of the field to date.

It is hoped that this collection will also help inspire an increase in interest in research in this area as it is clear that this is a blossoming field with the best yet to come and also the real possibility of creating new and effective therapies for hitherto very difficult to treat neuropsychiatric disorders such as treatment resistant depression and schizophrenia, among others.

Joseph R. Moskal

Joseph R. Moskal
(Guest Editor)

Falk Center for Molecular
Therapeutics, Northwestern University, Department of Biomedical
Engineering, 1801 Maple Ave., Suite 4300, Evanston, IL, 60201
Tel: (847) 491-4802
Fax: (847) 491-4810
E-mail: j-moskal@northwestern.edu