Editorial: Etiological Hypotheses of Mental Disorders at the Molecular Level

The last decade has brought up novel methodologies and increased volume of research in the field of translational science in psychiatry. We regard it timely and highly important to bring to the readership of the Israel Journal of Psychiatry an updated review of neurobiological aspects of psychosis and affective disorders written by worldwide experts. Obviously this issue provides just a glance into the wide range of topics currently studied focusing on etiological hypotheses of mental disorders at the molecular level. The review papers in this issue deal with molecular and genetic factors possibly contributing to the propensity for psychosis and affective disorders and to the development of novel treatment strategies.

Three different etiological hypotheses of psychotic disorders are presented by Drs. Javitt, Deutsch et al. and Waddington Lamont et al. Dr. Javitt elaborates on the involvement of the glutamatergic-NMDA neurotransmission system in schizophrenia and its treatment. He starts with an eloquent description of the induction of schizophrenia related symptoms by NMDA receptor blockers, continues with an integration of the glutamate hypothesis with the dopamine and GABA hypotheses of schizophrenia, and finally summarizes results of clinical trials with NMDA agonists (glycine, D-serine, etc.). Dr. Deutsch and his colleagues present the concept of potential GABAergic intervention in impaired high executive functions in schizophrenia. Their hypothesis is based on evidence that specific inhibitory GABA inter-neurons in the frontal cortex interact with, and affect oscillations of intermittent pyramidal neurons critical for high cortical functions such as working memory. Intermittent unsustained GABAergic intervention is a challenge for future antipsychotic treatment development. Dr. Waddington Lamont et al. focus on molecular clock mechanisms. Sleep disturbances are common in psychiatric disorders, in general, and in psychotic disorders, in particular. They present evidence that prolonged sleep deprivation induces hallucinations and psychotic symptoms reminiscent of schizophrenia, and that a relationship between the sleep-wake cycle and changes in mood is apparently important in bipolar disorder. Indeed, genetic studies found associations of the circadian rhythm genes CLOCK, PER1, PER3, and TIMELESS with schizophrenia and bipolar disorder.

Three different etiological hypotheses of affective disorders are presented by Drs. Weinstock, Klein, Agam and colleagues, Oxenkrug and Hanff and Minor. Dr. Weinstock emphasizes the contribution of environmental factors such as intrauterine exposure to stress in the increased vulnerability to major depressive disorder (MDD). Studies in animal models show that following chronic inescapable stress, prenatal stress or alcohol consumption the excess release of corticotropin-releasing hormone (CRH) and cortisol reduces birth weight and impairs the feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis and the signaling via the 5-HT1A and 5-HT2A receptors, and induces alterations in sleep and circadian rhythms. These changes, reversed by antidepressants, are reminiscent of symptoms in patients with MDD. The following two papers deal with the serotonergic hypothesis of affective disorders focusing on the serotonin precursor, the essential amino acid tryptophan. Drs. Klein, Agam and colleagues review human studies using the tryptophan depletion paradigm in healthy subjects, in untreated remitted or non-remitted and treated remitted MDD patients and in euthymic as well as manic bipolar patients. While in MDD diagnosed patients tryptophan depletion was generally associated with exacerbation of depression, manic patients benefited from short-term tryptophan depletion. The tryptophan depletion paradigm, which results in reduced brain serotonin, opens a window to the complex relationship between serotonin and mood disorders. Dr. Oxenkrug raises an alternative mechanism for serotonin deficiency in depression. He argues that metabolism of tryptophan is shunted away from serotonin production towards kynurenine production. Both stress hormones and pro-inflammatory cytokines, implicated in depression, activate the rate-limiting enzymes of kynurenine formation. The neurotropic activity of kynurenines suggests that the upregulation of the tryptophan–kynurenine pathway

not only augments serotonin deficiency but also underlies depression-associated anxiety, psychosis and cognitive decline. Drs. Hanff and Minor present the concept of possible interrelationship between organic malady and mood disorders. In particular, they elaborate on conservation-withdrawal, characterized by lethargy, hypoactivity, decreased libido, anorexia, anhedonia and increased sleep. It accompanies infectious disease, after-reaction to traumatic stress and recuperation from injury, but is also an integral component of major depression and related mood disorders. Drs. Hanff and Minor further review the role of the pro-inflammatory cytokine interleukin-1β (IL-1β) and its ability to recruit adenosine signaling at adenosine A2A receptors in mediating symptoms of conservation-withdrawal in illness as well as depressive behavior.

Although the etiology of psychotic and affective disorders is as yet not unraveled, heritable contribution for their phenotype is strongly supported by twin, adoption, familial and population studies. Dr. Segman and his colleagues review the current literature of genes possibly conferring risk for mental disorders and the genetic methodologies employed for their discovery. Recent advances in the field of genetics of complex disorders, such as non-hypothesis-driven genome-wide association studies in large cohorts, is suggested to hopefully overcome the scarcity of replications of risk genes reported thus far. In addition to single nucleotide polymorphism (SNP) variations reported in psychiatric disorders, which contribute a minute relative risk, the authors also discuss recent findings of copy number variations (CNVs) observed in rare cases but holding a very high relative risk for carriers. This special issue closes with a short commentary by Dr. Benjamin that challenges the odds to unravel the biological mechanisms of mental disorders. Regardless, the massive efforts invested so far towards the discovery of the pathophysiology of mental disorders have a heuristic value and will potentially culminate in better understanding and more adequate treatment modalities.

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