2nd Draft

The Endocrine System in Neuro-Developmental & Psychiatric Disorders

- **Maternal Immune Activation**
- **Endocrine Disrupting Chemicals**
- **Relationship of Microglia & the Immune System to Endocrine Dysregulation in both Maternal Immune Activation and Endocrine Disrupting Chemicals**

History

The Historical Development of Immunoendocrine Concepts of Psychiatric Disorders and Their Therapy.

Internationational Journal of Molecular Science (2015).

Abstract

Relationships between the central nervous, immune and endocrine systems are a focus of psychiatric research, particularly in depression and schizophrenia.

The field has long antecedents. Observed phenomena attributable to these relationships date back to the Neolithic era.

Immunoendocrine theories in the broadest sense are recorded in antiquity.

In the 19th century, Kraepelin and Wagner-Jauregg reported pioneering clinical observations in psychiatric patients.

Von Basedow, Addison and Cushing described psychiatric symptoms in patients suffering from endocrine diseases.

The 20th century opened with the identification of hormones, the first, adrenaline, chemically isolated independently by Aldrich und Takamine in 1901.

Berson and Yalow developed the radioimmunoassay (RIA) technique in 1959 making it possible to measure levels of hormones and cytokines.

These developments have enabled great strides in psychoimmunoendocrinology.

Contemporary research is investigating diagnostic and therapeutic applications of these concepts, for example by identifying biomarkers within the endocrine and immune systems and by synthesizing and testing drugs that modulate these systems and show antidepressant or antipsychotic properties.

Maternal Immune Activation

Influence of innate immune activation on endocrine and metabolic pathways in infancy.

Journal of Physiology, Endocrinology & Metabolism (2021)

The body of the article has a plethora of helpful information.

IMMUNE-NEUROENDOCRINE CROSS TALK

Interactions between the neuroendocrine and immune systems were discovered in the 1930s.

It is now well accepted that cross talk between these systems plays a vital role in controlling the duration and magnitude of the inflammatory response, as well as homeostatic physiological functions of the body during infection.

Bidirectional communication occurs between the immune and neuroendocrine systems systemically at the level of the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-gonadal (HPG) axis, and the hypothalamic-pituitary-thyroidal (HPT) axis.

In addition to these classical pathways, hormones that regulate feeding behavior and the renin-angiotensin-aldosterone system, among others, are modulated by immune activation and play a part in immunological function.

Activation of the maternal immune system induces endocrine changes in the placenta via IL-6.

Brain, Behavior and Immunity (2011).

Abstract

Activation of the maternal immune system in rodent models sets in motion a cascade of molecular pathways that ultimately result in autism- and schizophrenia-related behaviors in

offspring. The finding that interleukin-6 (IL-6) is a crucial mediator of these effects led us to examine the mechanism by which this cytokine influences fetal development in vivo.

Here we focus on the placenta as the site of direct interaction between mother and fetus and as a principal modulator of fetal development.

We find that maternal immune activation (MIA) with a viral mimic, synthetic doublestranded RNA (poly(I:C)), increases IL-6 mRNA as well as maternally-derived IL-6 protein in the placenta.

Placentas from MIA mothers exhibit increases in CD69+ decidual macrophages, granulocytes and uterine NK cells, indicating elevated early immune activation.

Maternally-derived IL-6 mediates activation of the JAK/STAT3 pathway specifically in the spongiotrophoblast layer of the placenta, which results in expression of acute phase genes.

Importantly, this parallels an IL-6-dependent disruption of the growth hormone-insulin-like growth factor (GH-IGF) axis that is characterized by decreased GH, IGFI and IGFBP3 levels.

In addition, we observe an IL-6-dependent induction in pro-lactin-like protein-K (PLP-K) expression as well as MIA-related alterations in other placental endocrine factors.

Together, these IL-6-mediated effects of MIA on the placenta represent an indirect mechanism by which MIA can alter fetal development.

Can Ashwagandha Benefit the Endocrine System?-A Review.

International Journal of Molecular Science (2023)

Particularly interesting are its properties reported in the field of psychiatry and neurology: in Alzheimer's disease, Parkinson's disease, multiple sclerosis, depression, bipolar disorder, insomnia, anxiety disorders and many others. The aim of this review is to fi …

Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome.

Kemp DE, et al. Bipolar Disord. 2010. PMID: 20636638

Neuroendocrine Stress System in Bipolar Disorder.

Current Top Behavioral Neuroscience (2021)

Different psychopathologies underlying **bipolar** disorders are supposed to involve persistent dysfunctions in the expression and role of both MR and GR in the hippocampus. We review and analyze the evidence related to the correlation between **bipolar** disorders and the …

Corticotropin-releasing hormone, microglia and mental disorders.

International Journal of Immunopathology Pharmacology (2014).

Microglia cells express corticotropin releasing **hormone** (CRH) receptors, and activation of **microglia** by CRH releases bioactive molecules which have a biological effect in the brain and regulate several neurological diseases. ...CRH also up-regulates IL-18 exp …

bstract

Microglia derive from mononuclear myeloid progenitors and are a major glial complement of the central nervous system.

When microglia are activated they secrete inflammatory cytokines and toxic mediators which amplify the inflammatory response.

In addition, the microglia inflammatory products are implicated in the neuronal destruction usually observed in various neurodegenerative diseases.

Microglia cells express **corticotropin releasing hormone (CRH)** receptors, and activation of microglia by CRH releases bioactive molecules which have a biological effect in the brain and regulate several neurological diseases.

CRH plays a pivotal role in stress responses and is a key mediator of the hypothalamicpituitary-adrenocortical system.

CRH is expressed in human mast cells, leading to autocrine effects and participates in inflammatory response together with neuropeptides, and stimulates mast cells.

IL-33-activated mast cells release vascular endothelial growth factor in response to CRH and act synergistically to increase vascular permeability.

CRH also up-regulates IL-18 expression by increasing intracellular reactive oxygen in **microglia cells.**

Here we report the relationship between CRH, microglia and mental disorders.

Microglia: Neuroimmune-sensors of stress.

Seminar Cell Developmental Biology (2019).

Microglia express a diverse array of receptors, which also allows them to respond to stress **hormones** derived from peripheral as well as central sources. Here, we review studies of how exposure to acute and chronic stressors alters the immunophenotype and function of …

Endocrine Disruptors

The research landscape concerning environmental factors in neurodevelopmental disorders: Endocrine disrupters and pesticides-A review.

Frontiers in Neuroendocrinology. 2024

In recent years, environmental epidemiology and toxicology have seen a growing interest in the environmental factors that contribute to the increased prevalence of neurodevelopmental **disorders**, with the purpose of establishing appropriate prevention strategies. A literatur …

Editorial: Endocrine disruptors and diseases of brain and mind: past and prelude.

Frontiers in Endocrinology (Lausanne). 2024

Endocrine disruptors or endocrine disrupting chemicals (EDCs) are structurally diverse synthetic and naturally occurring compounds that interfere with the endocrine system with potentially adverse health outcomes.

Relatively low concentrations of EDCs persist in the environment and produce long-term alterations percolating from generation to generations.

Exposure to EDCs is associated with cancer, stillbirth or birth defects, developmental disorders, metabolic changes, and is increasingly suspected in the sporadic occurrences of neurological and neuropsychiatric disorders.

Linking Environmental Chemicals to Neuroinflammation and Autism Spectrum Disorder: Mechanisms and Implications for Prevention.

Molecular Neurobiology. 2024

Abstract

This article explores the potential link between endocrine-disrupting chemicals (EDCs), neuroinflammation, and the development of autism spectrum disorder (ASD).

Neuroinflammation immune function in the brain, leading to chronic or excessive neuroinflammation.

This disruption of immune function can contribute to developing neurological disorders, including ASD.

Furthermore, EDCs may activate microglia, increasing pro-inflammatory cytokine production and astroglia-mediated oxidative stress, exacerbating neuroinflammation.

EDCs may also modulate the epigenetic profile of cells by methyltransferase expression, thereby affecting neurodevelopment.

This article also highlights the importance of reducing exposure to EDCs and advocating for policies and regulations restricting their use.

Further research is needed to understand better the mechanisms underlying the link between EDCs, neuroinflammation, and ASD and to develop new treatments for ASD.

Lithium and endocrine disruption: A concern for human health?

Environment International. 2024

Lithium is a key medication for the treatment of **psychiatric disorders** and is also used in various industrial applications (including battery production and recycling). Here, we review published data on the **endocrine**-disrupting potential of lithium . . .

Our results show that lithium meets the World Health Organization's definition of a thyroid hormone system disruptor - particularly when used at therapeutic doses.

When combined with knowledge of adverse outcome pathways linking molecular initiating events targeting thyroid function and neurodevelopmental outcomes, the neurodevelopmental data reported in animal experiments prompt us to suggest that lithium influences neurodevelopment.

However, we cannot rule out the involvement of additional modes of action (i.e. unrelated to the thyroid hormone system) in the described neural effects.

Given the increasing use of lithium salts in new technologies, attention must be paid to this emerging pollutant - particularly with regard to its potential effects at environmental doses on the thyroid hormone system and potential consequences on the developing nervous system.

Prenatal endocrine-disrupting chemicals exposure and impact on offspring neurodevelopment: A systematic review and meta-analysis.

Neurotoxicology. 2024

Conclusion: Prenatal exposure to EDCs (Endocrine Disrupting Chemicals_, especially metals, phthalates and, poly-fluoroalkyl substances, was associated with disrupting the development of offspring neurobehavior in the short and long term. Additionally, cognitive development showed gender differences due to prenatal endocrine-disrupting chemicals exposure

Bisphenol A and microglia: could microglia be responsive to this environmental contaminant during neural development?

American Journal of Physiology, Endocrinology and Metabolism. 2018

One such challenge that is newly arising in this field is whether **microglia** might be downstream targets to **endocrine**-disrupting chemicals, such as the plasticizer bisphenol A (BPA), which functions in part by mimicking estrogen structure and function. ...Mechanistic …

Miscellaneous

ADHD symptoms and diurnal cortisol in adolescents: The importance of comorbidities.

Psychoneuroendocrinology. (2023)

BACKGROUND: Altered regulation of diurnal **cortisol** has been associated with both dimensional symptoms and clinical diagnoses of **attention deficit**-**hyperactivity disorder** (**ADHD**). Indeed, a recent meta-analysis suggests that lower diurnal …