Neurobiology of Addiction

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Disclosure

• Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose
DEFINITION OF ADDICTION

• A CHRONIC, RELAPSING CONDITION
• A COMPULSION TO SEEK AND TAKE DRUGS
• LOSS OF CONTROL OF DRUG USE
• IF UNABLE TO OBTAIN/USE DRUG RESULT IS DISTRESS, ANXIETY, DEPRESSION
THREE STAGE CYCLE (KOOB ET AL)

- BINGE/INTOXICATION
- WITHDRAWAL/NEGATIVE AFFECT
- PREOCCUPATION/ANTICIPATION
INCREASES PRODUCE NEGATIVE AFFECT

• CRF
• NE
• DYNORPHIN
• VASOPRESSIN
• OREXIN
• SUBSTANCE P
DECREASES PRODUCE NEGATIVE AFFECT

• NEUROPEPTIDE Y
• NOCICEPTIN
• ENDOCANNABINOIDS
ALLOSTASIS

• NEW SET POINTS OUTSIDE THE HOMEOSTATIC RANGE
• CHANGES MOST IMPORTANT ARE THOSE IN STRESS AND REWARD
• INVOLVES CHANGES IN HPA AXIS
ALTERATIONS OF THE HPA AXIS IS CENTRAL TO MODERN THEORIES
HPA AXIS

GHRH, TRH, CRH, PRH, GNRH

Hypothalamus

Neurons that produce hormones released from posterior pituitary

Pituitary stalk

TSH, FSH, LH, PRL, GH, ACTH, ALPHA-MSH

Anterior pituitary

Posterior pituitary

VASOPRESSIN, OXYTOCIN

SOMATOSTATIN
STRESS, ANXIETY, HPA AXIS, AND ADDICTION

• RELATIONSHIP COMPLEX
• ACUTE STRESS ACTIVATES HPA WITH RELEASE OF CRF, ACTH, CORTISOL
• CHRONIC STRESS ADAPTIVE CHANGES OCCUR
• FEEDBACK INHIBITION OF GLUCOCORTICOID RECEPTORS, DOWNREGULATION OF POSTSYNAPTIC NE RECEPTORS AND UPREGULATION OF INHIBITORY AUTO-RECEPTORS AND HETERO-RECEPTORS ON PRESYNAPTIC NEURONS
COMPLEX AND VARIABLE

• SOME STRESS CAN LEAD TO LOWER CORTICOSTERONE LEVELS, OTHERS IT IS INCREASED

• EVEN SOME TIME LIMITED STRESSORS LEAD TO LONG LASTING HPA CHANGES

• ANIMAL MODELS SHOW THAT PRENATAL STRESS OR EARLY MATERNAL DEPRIVATION LEAD TO INCREASED CORTICOSTERONE RESPONSE INTO ADULTHOOD
NEUROENDOCRINE FUNCTION AND DEPRESSION

STRESS

INCREASED CRF

INCREASED POMC

INCREASED ACTH

DECREASED BETA ENDORPHIN

INCREASED GLUCOCORTICOID

INCREASED GLUTAMATE
NEUROENDOCRINE FUNCTION AND DEPRESSION CASCADE

RED ARROWS INHIBITION
BLUE ARROWS STIMULATE

STRESS

INCREASED CRF

5-HT

INCREASED ACTH

GABA

INCREASED POMC

INCREASED GLUCOCORTICOID

INCREASED GLUTAMATE

NE

5-HT

PROLACTIN

DOPAMINE

GLUTAMATE

INCREASED POMC

DECREASED BETA ENDORPHIN

DECREASED SOMATOSTATIN, GH, NEUROTROPHIC FACTORS, SYNAPTIC GLUTAMATE INCR

NE AUTO-RECEPTORS

SYMPATHETIC NERVOUS SYSTEM
Paraventricular Nucleus Synthesizes CRF (also called CRH)
LIMBIC CORTICAL STRIATAL PALLIDAL THALAMIC TRACT AND DEPRESSION

- HIPPOCAMPUS
- AMYGDALA
- CAUDATE NUCLEUS
- PUTAMEN
- FRONTAL CORTEX
RECENT CONTRIBUTIONS TO SUSCEPTIBILITY

• STRUCTURAL AND FUNCTIONAL CHANGES IN THE BRAIN
BRAIN AREAS OF INTEREST IN ADDICTION

IMAGING STUDIES INDICATE HYPERACTIVITY OF AMYGDALA AND SUPRA ANTERIOR CINGULATE GYRUS, WHEREAS DLPFC AND SUBGENUAL ANTERIOR CINGULATE GYRUS ARE HYPOACTIVE. NACC ANOTHER DBS TARGET
VOLUME LOSS IN LCSPT

- ADDICTION ASSOCIATED WITH VOLUME LOSS IN LCSPT STRUCTURES, ESPECIALLY HIPPOCAMPUS WITH HYPERCORTISOLEMIA
- VOLUME LOSS IN ONE STRUCTURE AFFECTS ENTIRE PATHWAY
HPA, CRF, ADDICTION

• HPA IS PRIMARY NEUROENDOCRINE STRUCTURE MEDIATING STRESS RESPONSE

• CRF (ALSO CALLED CRH) IS PRODUCED IN THE PVN OF THE HYPOTHALAMUS

• CRF ACTS ON CRF-1 AND CRF-2 RECEPTORS IN CNS AND ANTERIOR PITUITARY
THE ROLES OF CRF 1 AND 2

• CRF-1 MEDIATES ANXIETY, DEPRESSION, AND STRESS RESPONSE

• ROLE OF CRF-2 IS NOT FULLY ELUCIDATED. SOME BELIEVE IT a) COUNTERACTS ROLE OF CRF-1 OR b) CRF-2 IS ACTIVATED BY INESCAPABLE STRESSORS WHILE CRF-1 IS ACTIVATED BY ESCAPABLE STRESSORS
DOWNSTREAM EFFECTS

• CRF IS A MAJOR REGULATOR OF BASAL AND STRESS INDUCED POMC AND POMC-INDUCED PEPTIDES (BETA ENDORPHIN AND ACTH) FROM ANTERIOR PITUITARY

• ACTH ACTS ON ADRENAL CORTEX TO PROMOTE SYNTHESIS AND RELEASE OF CORTISOL AND OTHER GLUCOCORTICOIDS
MORE DOWNSTREAM EFFECTS

• GLUCOCORTICOIDS INHIBIT RELEASE OF CRF AND ACTH

• GABA INPUTS FROM THE HIPPOCAMPUS INHIBIT THE STRESS RESPONSE BY DECREASING CRF SYNTHESIS IN THE CENTRAL NUCLEUS OF THE AMYGDALA
FARTHER DOWNSTREAM

• AMYGDALA AND HIPPOCAMPUS SEND SEROTONIN, GABA, AND ACETYLCHOLINE INPUTS TO AFFECT SECRETION OF ACTH

• SEROTONIN NEURONS TERMINATE ON INHIBITORY GABA NEURONS TO BLOCK GABA INHIBITION OF CRF SYNTHESIS

• DAMPENED GABA ACTIVITY ENHANCES CRF EXPRESSION IN AMYGDALA AND ACTIVATES NE SYSTEM

• THUS GABA PROBABLY PLAYS A TONIC ROLE IN HPA AXIS MODULATION
WHAT CAN WE SAY ABOUT HPA AXIS AND ADDICTION?

• MANY DIFFERENT MECHANISMS OF VULNERABILITY
  – INCREASED SECRETION OF HORMONES IN THE CASCADE
  – DECREASED SENSITIVITY TO NEGATIVE FEEDBACK
  – ALTERED REGULATORY FUNCTION OF CRF IN REDUCING LOCUS COERULEUS AND PVN
NEURONAL PLASTICITY AND BDNF

• BDNF IS DOWNSTREAM TARGET OF c-AMP PATHWAY

• REGULATES NEURONAL SURVIVAL AND SYNAPTIC PLASTICITY DURING DEVELOPMENT AND ADULTHOOD

• STRESS IS ASSOCIATED WITH DECREASED BDNF AND SERUM LEVELS LOWER IN SOME ADDICTION---MAY INCREASE WITH ABSTINENCE
ABSTINENCE INCREASES BDNF IN SOME STUDIES

INCREASES Gs COUPLING TO ADENYL CYCLASE WHICH INCREASES c-AMP

AS A RESULT THERE ARE INCREASES IN CALCIUM DEPENDENT KINASES, WHICH LEADS TO INCREASED EXPRESSION OF c-AMP RESPONSE ELEMENT BINDING PROTEIN (CREB)

CREB INCREASES BDNF IN LIMBIC STRUCTURES AND HIPPOCAMPUS AND INCREASES EXPRESSION OF THE BDNF RECEPTOR TrkB

LIKELY THAT OTHER GROWTH FACTORS ARE ALSO INVOLVED
SEROTONIN AND THE HPA AXIS

• 5-HT CAN STIMULATE CRF RELEASE MEDIATED BY 5-HT2, 5-HT1A, AND 5-HT1C RECEPTORS

• GLUCOCORTIOIDS INCREASE 5-HT FUNCTION IN ANIMAL MODELS

• ACUTE STRESS INCREASES 5-HT RELEASE transiently but CHRONIC STRESS LEADS TO 5-HT DEPLETION, INCREASE 5-HT1A AUTORECEPTOR PRODUCTION FURTHER REDUCING 5-HT FUNCTION

• IMAGING STUDIES CONTRADICTORY
SEROTONIN RECEPTORS

• 14 GENETICALLY DISTINCT, 7 FAMILIES TERMED 5-HT1 THROUGH 5-HT7
• CELL BODIES AND DENDRITES OF SEROTONIN NEURONS LOCATED MAINLY IN RAPHE AND MIDBRAIN PROJECTING TO ALMOST ALL BRAIN REGIONS AND SPINAL CHORD
• EXCEPTIONS ARE SEROTONIN NEURONS TO CEREBELLUM THAT ORIGINATE IN N. RETCULARIS PARAGIGANTOCELLULARIS AND N. PONTIS ORALIS OF BRAINSTEM
Dopamine Pathways

Frontal cortex

Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine-tuning)
- Compulsion
- Perseveration

Serootonin Pathways

Striatum
Substantia nigra

Functions
- Mood
- Memory processing
- Sleep
- Cognition

Nucleus accumbens
VTA
Hippocampus
Raphe nucleus
2 Glutamate Receptors

- Ionotropic Receptors
  - Directly gated channels
  - Always excitatory

- Metabotropic Receptors
  - In-directly gated channels through second messengers
  - Excitatory or inhibitory
**Ionotropic receptor**

Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (From Kandel et al., 1991).

**Metabotropic receptor**

Fig. 5b. Metabotropic receptors are coupled to their associated ion channels by a second messenger cascade (top). Each mGluR is composed of one polypeptide, which is coupled to a G-protein (from Kandel et al., 1991).
Pathological Activation of NMDA Receptors

Pathological Activation of NMDA Receptors

Impairment of Plastic Processes

Neurodegeneration

Rest

Cognitive Activity

Signal Not Detected

Damaged Neurons

\[ \text{Ca}^{2+} \] (Calcium)

Noise

Signal Noise

\[ \text{Glutamate} \]

\[ \text{Mg}^{2+} \] (Magnesium)

Adapted from Parsons CG et al. Neuropharmacology. 1999; 38:735.
• SOME DEPRESSED PATIENTS HAVE INCREASED LEVELS OF INFLAMMATORY MARKERS IN BLOOD AND CSF

• IL-1, IL-6 TNF NUCROSIS FACTOR-ALPHA, C-REACTIVE PROTEIN, CHEMOKINES

• CYTOKINES DECREASE NEUROTRANSMITTER FUNCTION (SEROTONIN), DECREASE GLUCOCORTICOID SENSITIVITY, BLOCK NEUROPLASTICITY
SUBSTANCE P

• ACTIVATES NK1, NK2, NK3 RECEPTORS
• NK1 RELATED TO ADDICTION
• BUT NK1 ANTAGONISTS LACKING EVIDENCE OF EFFICACY