Allostatic Load

How Psychiatric Drugs Stress the Brain & Body

Presented by Grace E. Jackson, MD
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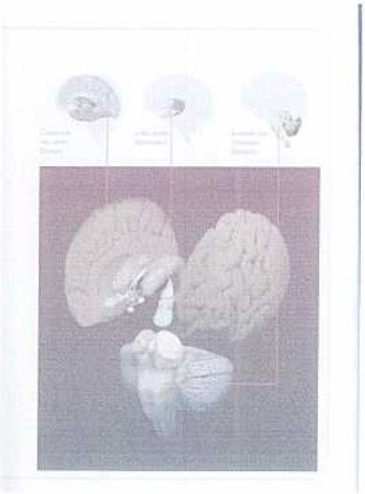
The Human Brain

MacLean's Triune Brain

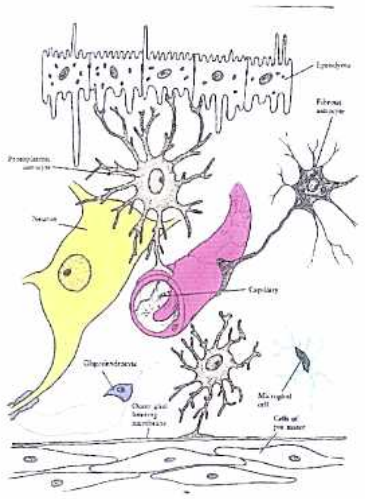
- reptilian
- mammalian
- neo-mammalian



The Cells of the Brain

- 500 billion to 1 trillion glia
- Four types of glia:

  - ependymal cells
  - astrocytes
  - oligodendrocytes
  - microglia

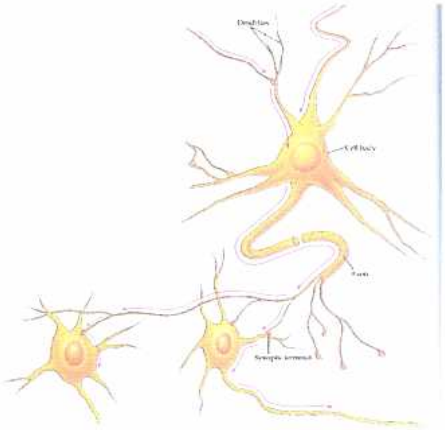


The Cells of the Brain

- 100 billion neurons
- 1000 connections

Main components:

- dendrites
- soma
- axon
- nerve terminal (bouton)



The Function of the Neuroglia

- Provide structural support
- Provide nutrients / energy
- Detoxify potentially harmful chemicals
- Fight infection
- Maintain the integrity of the Blood Brain Barrier

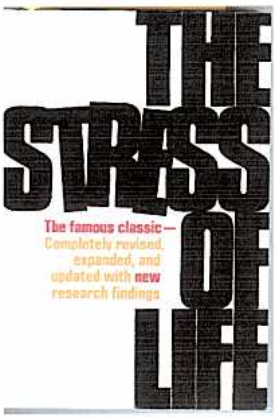
The Function of the Neurons

- to send and receive electrical and chemical messages

- chemical messages = neurotransmitters

  - dozens of neurotransmitters exist
  - very few have been well studied

Good Stress vs. Bad Stress



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What do psychiatric drugs do ?

- psychiatric drugs enter the brain
- create complex changes inside the cells to which they have bound
- alter the function and/or structure of the brain

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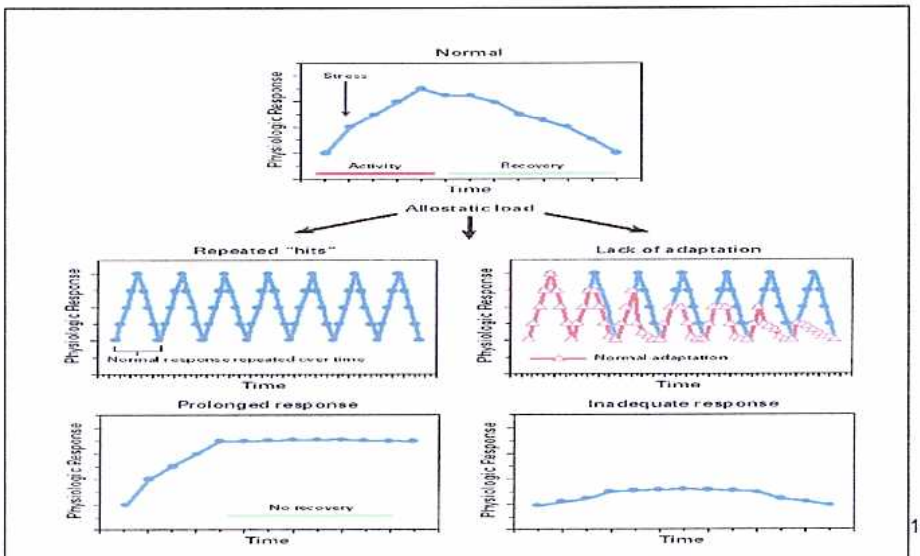
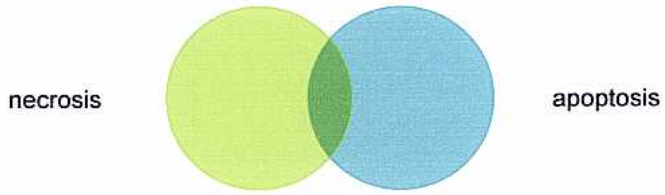
How Drugs Create Stress



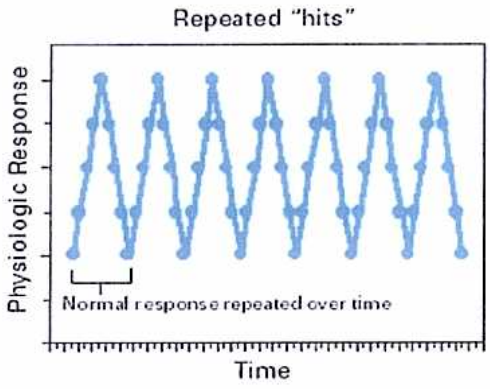
Dr. Bruce McEwen: Allostatic Load

- homeostasis = stability in normal physiological states of an organism
- allostasis = viability through change [eustress]
- allostatic load = prolonged or maladaptive responses to internal or external stimuli [distress]

Neurotoxicity



Type I Repeated Hits



Necrosis
terrorist attack

- Defects in membrane permeability
- Impairment in oxidative phosphorylation
- Depletion of high energy phosphates
- Organelles undergo swelling
- Ribosomes are dispersed from rough ER
- Nuclei of dying cells condense
  into many irregularly shaped clumps

Necrosis

necrosis

Apoptosis
controlled demolition

- Earliest changes occur in the nucleus
- Chromatin condenses into sharply delineated, uniformly dense masses
- Cytoplasm condenses, darkens
- Vacuoles form from Golgi or ER
- Mitochondria remain normal until late
- Nuclear and plasma membranes deteriorate
- Cellular debris buds off (apoptotic bodies)

Apoptosis

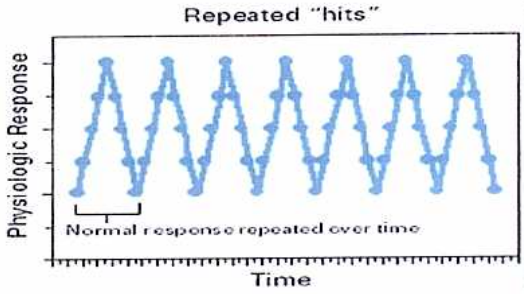
apoptosis

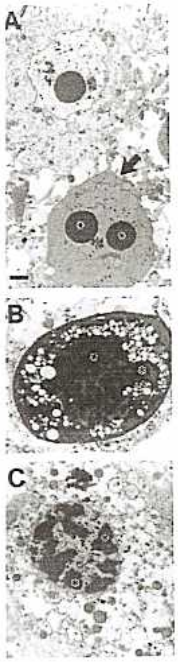
Type I
Repeated Hits

- repeated dosing of Haldol

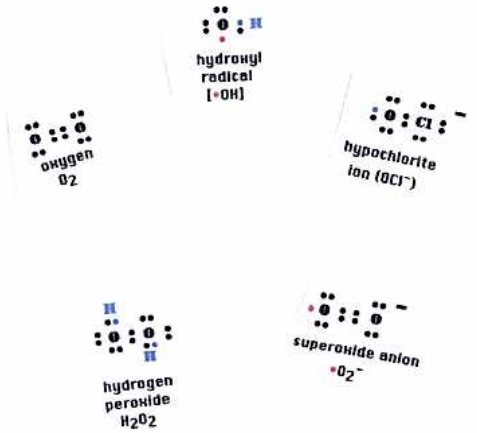
each exposure leads to generation of reactive oxygen species

haloperidol and HPTP (h. tetrahydropyridine) are transformed into HPP+ (haloperidol pyridinium) RHPP+ (reduced h. pyridinium)





Examples of Reactive Oxygen Species



Psychiatric Drugs Can Generate Free Radicals

- free radical = molecule with one or more unpaired electron in its outer orbital
- highly unstable (reactive) molecules
- donate, steal, or share outer orbital electron causing chain reactions of free radicals
- oxygen based molecules are called ROS
  Reactive Oxygen Species

Reactive Oxygen Species
Negative Aspects

ROS react with sugars, lipids, proteins

- weakening cell membranes
- degrading protein:
  loss of protein structure and function
- directly damaging DNA
- end result: necrosis and/or apoptosis

Reactive Oxygen Species
Positive Aspects

- oxidative phosphorylation to produce ATP (energy)
- immune system:
  - macrophages use superoxide dismutase to convert superoxide ion to H202
  - neutrophils use myeloperoxidase to convert H202 with CL^- to hypochlorite [bleach]
- cell signalling: nitric oxide
- production of thyroxine by thyroid gland (uses H202)

Tissue Transglutaminase

- Graz, Austria study (Bonelli et al, 2005)

➢ Researchers examined spinal fluid of 29 patients exposed to neuroleptic (old and new) therapy (8 with AD, 21 with other neurological diseases) vs. 55 without NL

➢ Findings: atypicals did not differ from "typical" NL with respect to tTG proteins in CSF

Psychiatric drugs can damage cells by inducing apoptosis directly. . .

Antipsychotics
Apoptosis in humans ?

- above average tTG:

melperone	4.78 ng/dL
zotepine	8.78 ng/dL
olanzapine	8.50 ng/dL
flupentixol	7.86 ng/dL
haloperidol	7.30 ng/dL

Austrian Study: ? Apoptosis
Tissue Transglutaminase

	Alzheimer's dementia n = 33		non AD n = 51	
	no drug	drug	no drug	drug
tTG ng/dL	5.45	14.21	1.04	5.72

* drug = neuroleptic, old or new

Jellinger (1977) Neuropathology Study

Drugs included…

chlorpromazine
trifluoroperazine
reserpine
thioridazine
chlorprothixene
TCAs
tranquilizers

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Kurt Jellinger (1977) Neuropathology After NL Therapy

- examined brains of 28 individuals (16 males, 12 females)
- age range: 21-74
- average age at death: 56
- average NL exposure: 5 years (range: 2 months to 11 years) INTERMITTENT exposure

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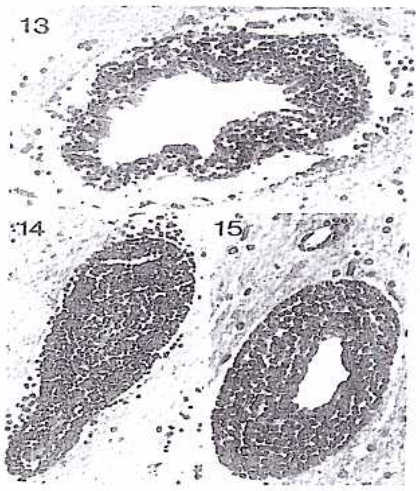
Other Abnormalities: cerebral phlebitis

- Three patients had inflammation of the cerebral veins

Photo shows white cells lining walls of veins in striatum, thalamus, globus pallidus



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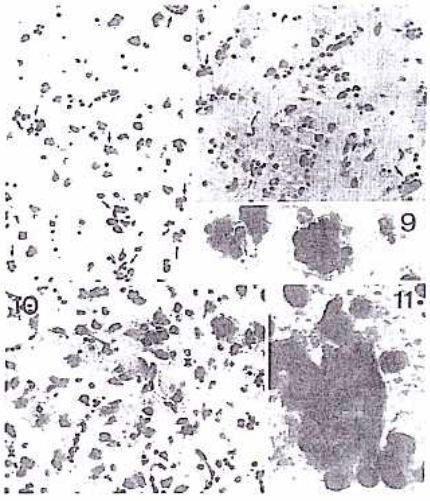
Changes in Basal Ganglia

46% of patients had abnormal changes in caudate

- swelling of large neurons
- increased glial satellitosis
- some patients had swollen axons in GP & chromatolysis in surrounding neurons



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Structural Changes Antidepressants

Results:

after 18 hrs of drug washout

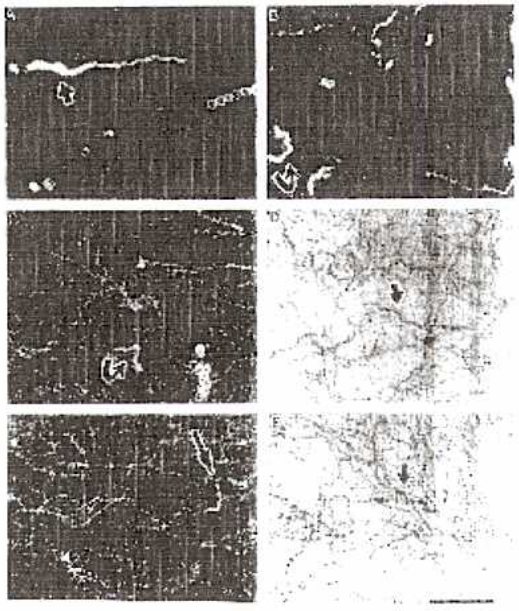
swollen and truncated
axons & corkscrew profiles
were seen in
frontal and occipital cortices,
hippocampus, and midbrain

Structural Changes After Antidepressants [Kalia et al, 2000]

- rats were exposed to SRIs or fenfluramine for four days [MDMA was the control]
- brains were examined for changes in rats immediately and after 30 day recovery period
- high and low doses were compared

Amphetamines (Ricuarte et al, 2005)

"Amphetamine Treatment Similar to That Used in the Treatment of Adult ADHD Damages Dopaminergic Nerve Endings in the Striatum of Adult Nonhuman Primates"



baboons/squirrel monkeys on speed

Findings:

- Significant reductions in striatal DA concentrations, DAT labeling, amount of DAT protein, VMAT2 labeling
- 44-47% depletion of DA in caudate/putamen
- 30% depletion in nucleus accumbens

Johns Hopkins Univ.

Would amphetamine similar to that used in therapy of adult ADHD produce long term effects on brain DA neurons in non-human primates ?

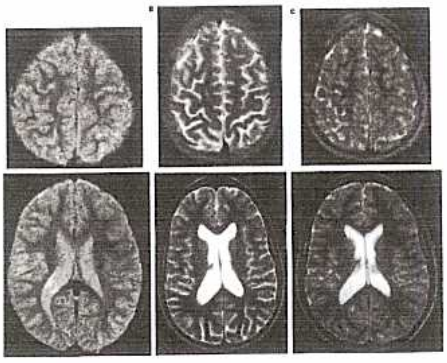
- 3:1 mixture of dextro- and levo-amphetamine similar to that in dextro-amphetamine
- animals were given amphetamine b.i.d. x 4 weeks 0.25 mg/kg x week 1, then 0.50 mg/kg for remainder

- Parkinsonism may not become clinically apparent until DA is reduced 80-90%
- Cognitive dysfunction: may be missed because of ADHD in patients receiving this drug [cognitive deficits get blamed on underlying condition]

Why relevant ?

- Doses administered corresponded to human dosing: 5 – 60 mg b.i.d.
- Plasma levels were obtained: mean plasma levels ranged from 100-150 ng/mL
- This was consistent with two studies which checked amphetamine plasma levels in children: 120-140 ng/mL

Depakote
Pseudoatrophy of the Brain

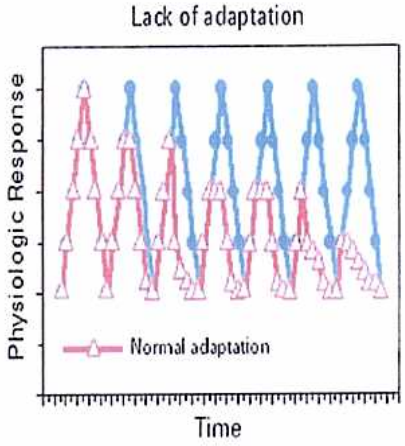


Mood Stabilizers

- VPA: depakote dementia
- Lithium: SILENT
- CBZ, OXC: low therapeutic index

Type II
Failure to Adapt

- REM sleep suppression
- prolonged elevations in PRL
- sensitization (not shown)



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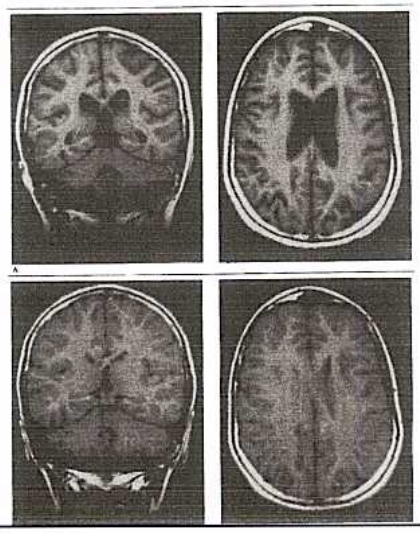
Depakote
Pseudoatrophy of the Brain



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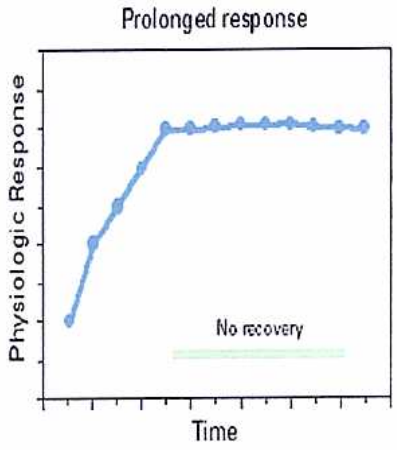
Type III
Prolonged Response After Drug

- HPA disruptions
- drug withdrawal
- drug rebound
- tardive phenomena



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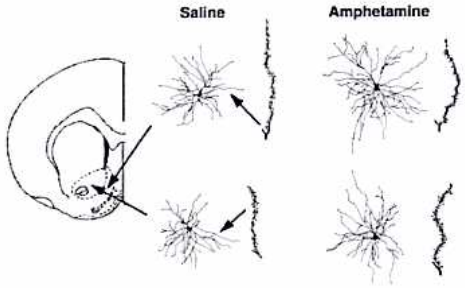
Sensitization to Stimulants

[Robinson & Kolb, 1997]

- amphetamines cause changes in structure of the brain [rats]
- increased density and branching of dendrites in the nucleus accumbens & prefrontal cortex
- decreased density and branching in other regions of neocortex

nucleus accumbens
5 wk exposure / 38 days recovery



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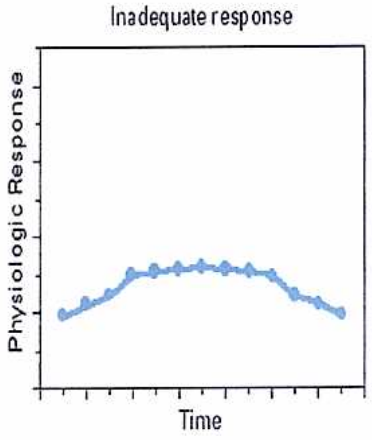
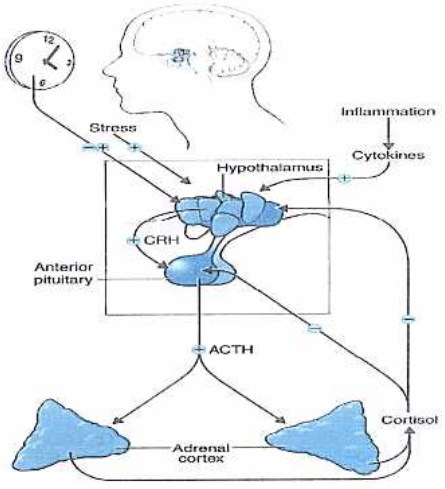
Type IV
Inadequate Response

- neuroleptic induced deficit syndrome
- tardive psychosis
- antidepressant induced suicidality
- kindling ?



HPA disruptions

- ? do ACTH and cortisol levels re-equilibrate
- ? are pulsatile surges in PRL harmful
- ? what disruptions in growth hormone and other trophic factors are sustained



Revised Monoamine Hypothesis of Depression

Serotonin depletion …

- 14 of 21 remitted patients on meds experienced rapid return of symptoms with 5HT depletion
- 100% of MAOi patients relapsed
- 63% of SSRI patients relapsed
- 18% of DMI (NRI) patients relapsed

Revised Monoamine Hypothesis of Depression [Heninger et al, 1996]

- healthy subjects experienced no depression in response to abrupt reductions in serotonin, NE, or DA
- unmedicated, currently depressed subjects did not experience any worsening of symptoms

Revised Monoamine Hypothesis of Depression

- Previously medicated, fully recovered patients (median remission: 30 weeks) exposed to 5HT depletion experienced average increase of 8 points on the HDRS
- Previously unmedicated patients experienced no effects, or only small effects, with 5HT depletion

Revised Monoamine Hypothesis of Depression

Catecholamine depletion . . .

- 8 of 19 recently remitted patients experienced rapid return of symptoms
- 90% of CRI patients (8 of 9) relapsed
- 0% (0 of 10) SSRI patients relapsed