Behavioural Bioassays in Neuroscience: 
Brain and Behavior From Invertabrates To Small Mammals

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ICIPE, Nairobi KENYA

Environmental Toxicity and 
Neurodegenerative Disease
NEURODEGENERATIVE DISEASES

● Neurodegeneration can be found in many different levels of neuronal circuitry

● Progressive loss of structure and function of neurons: Cell death

● Alteration of functions: cognition, memory, behavior, motor,…

● Handicap, exclusion, morbidity, death
EXEMPLES of NEURODEGENERATIVE DISEASES

- Spinocerebellar Ataxies
- Atrophy
- Epilepsy
- Leucoaraiosis
- Alexander Diseases
- Alpers Diseases
- Alzheimer Diseases
- Creutzfeldt-Jakob Diseases
- Huntington Diseases
- Parkinson Diseases
- Pick
- Sclerosis
- Amyotrophique Lateral Sclerosis
- X
- X
- X
- X
EPIDEMIOLOGY OF PARKINSON’S DISEASE

- Parkinson's disease together with Parkinsonism is the second most common neurodegenerative disorder in the population aged 50 and more
  - Exception in countries with short life expectancy
- Incidence: 8 - 18 cases per 100,000 persons/year
- Middle age: 60 years with 5-10% of early developed cases 20 - 50 years
- Exposure to environmental toxins increases the risk of PD
- More risk in rural zones with industry production of pesticides, heavy metals etc.
- More cases in men than women
## CLASSIFICATION of PD FORMS

<table>
<thead>
<tr>
<th>PARKINSON’S DISEASE</th>
<th>Idiopathique</th>
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| PARKINSONIAN’S SYNDROMES | Olszewski disease  
striato-Nigrale degeneration  
Cortico-basale degeneration  
Hallervorden-Spatz disease  
Wilson disease  
Shy-Drager syndrome  
Olivo-ponto-cerebellar Atrophy |
| SYMPTOMATIC PARKINSONISM | Toxin-induced (MPTP, carbone monoxide, manganese)  
Drug-induced (reserpine, calcium antagonists, neuroleptics  
Infectious (Encephalitis lethargica, luetic)  
Vacular trauma  
Brain carcinoma |

*J Sian et al., Basic Neurochemistry, 1999*
CARACTERISTICS OF PARKINSON’S DISEASE

- **Cardinal Symptoms (Motor)**
  - Tremor at rest
  - Muscle stiffness/Akinesya: difficulties in walking, writing, speaking, frozen facial expression
  - Bradykinesia: slowdown in the initiation and execution of movements
  - Instability in posture

- **Functional Disorders (Non Motor)**
  - Cognitive Functions
  - Humour
  - Automatic execution of planned motor tasks
  - Sexual Functions
  - Body Weight
  - Sleep Wake Cycle
Which Neurotransmitter is concerned?

- Motor Coordination in Complex Circuitry
PATHOPHYSIOLOGY OF PARKINSON DISEASE

Basal Ganglia

- Motor control
- Cognition
- Limbic Functions
Striatum

- Two types of neurons:
  - Projecting neurons: middle dendrite arborisation, GABA (SP, Dynorphines or Enk)
  - Interneurones GABA or Acetylcholine

Globus Pallidus

- Two Subdivisions:
  - Globus Pallidus External part: GABA
  - Globus Pallidus Internal part: GABA
**Subthalamic Nucleus**

- Small Structure with big projecting cells containing Glutamate
- The only excitatory structure of basal ganglia

**Substancia Nigra**

- Pars Compacta: DA
- Pars Reticulata: GABA
Basal Ganglia

- Interconnexion – connexion with thalamus & cortex

- Indoor structure receives input from cortex

- Outdoor structures send output to thalamus

- STN output is GLU

- Interconnexions are inhibitory
Executive Network

Principal: Integration of environmental stimuli

Two additional:
PATHOPHYSIOLOGY OF PARKINSON DISEASE

Modulatory Network
Basal Ganglia

- Interconnexion – connexion with thalamus & cortex

- Indoor structure receives input from cortex

- Outdore structures send output to thalamus

- STN output is GLU

- Interconnexion are inhibitory

PATHOPHYLOGLY OF PARKINSON DISEASE

Stimuli

Cortex cérébral

Glutamate

DA
PATHOPHYSIOLOGY OF PARKINSON DISEASE

Normal Substancia Nigra

DA / Neuromelanamine

α synuclein: Substancia Nigra

Loewi Body

Sub Thalamic Nucleus

Regular

Bursty

Parkinson Disease
PATHOPHYSIOLOGY OF PARKINSON DISEASE

- Sub Thalamic Nucleus

**CORTEX**

**Major Efferences**

**Indirect Pathway**

- **GPe**

**Direct Pathway**

- **Cd/Put**

**SNr/GPi**

The diagram illustrates the brain's key structures involved in Parkinson's disease pathophysiology, including the cortex, basal ganglia (GPe, Cd/Put, SNr/GPi), and thalamus (Thal). It highlights the movements facilitation and task programming processes, with a focus on the indirect and direct pathways. The subthalamic nucleus (STN) plays a crucial role in this process, with GABAergic and glutamatergic interactions. Regular and burst patterns of neural activity are depicted.
CAUSES & RISK FACTORS

• Causes: Not Yet Known
• Mutation of Genes (Park)

Risk Factors:

• Age
• Heredity 5%
• Sexe: Predisposal in male

• Prolonged Exposure to Toxins
• Exposition to Toxins: pesticides Rotenone, Heavy Metals, Others
ANIMAL MODELS OF PARKINSON’S DISEASE

Neurological disorders in humans can be modeled in animals using standardized procedures that recreate specific pathogenic events and their behavioral outcomes.

- 6-OHDA and MPTP Mice
- Nockout Mice
- 6-OHDA Rat
- MPTP Monkey
- α Synuclei Rat & Mice
- Rotenone Mice


Nigral iron elevation is an invariable feature of Parkinson's disease and is a sufficient cause of neurodegeneration. Ayton S, Lei P., Biomed Res Int. 2014


Erikson and Achner, Neurochemistry International, 2003
Toscano and Guirlante, Brain Res Review, 2005
Zhong et al., Neuroscience Letters 2010
Uversky et al. J. Biol. Chem. 2001
Banks et al., Neurotoxicology, 1997
DISORDERS INDUCED BY LEAD

- Body Weight
- Brain Development
- Learning and Memory
- Humour: Anxiety, Depression
- Sleep Wake Cycle
- Motor Functions
- Neurotransmitters: dopamine, noradrenaline, serotonine
- Cell Functions: inflammatory Processes and Oxidative Stress
- Hippocampal Neurogenesis
- ADN and Proteines denaturation
- etc.
MAJOR BRAIN HEALTH PROBLEMS IN MOROCCO

• More than 50,000 cases of Parkinson these last 10 years, 4000 new cases per year since 2010
• Entier Villages with extra pyramidal syndromes around metallurgic mines
• Alzheimer: 8.1% of the population aged 60 and more; 50,000 cases in 2010 (5%: >65; 10%>75; 20% >90)
• Saturnisme
• Cognitifs troubles
• Epilepsy
• Schizophrenia
• Cerebral Cancer (Glyomes) in children
Ouarzazate
Laâyoune
Zagora
HIGH incidence of Parkinsonism
High presence of extrapyramidal syndromes
Saturnisme

Lead Production
Mines Workers

Europe
Africa Continent

Saturn's
Tetuan
Rabat
Casablanca
Safi
Marrakech
Málaga
Gibraltor
Sevilla
Las Palmas de Gran Canaria
Tetuan
Ouïda
Europe
Africa Continent
HEAVY METAL INTOXICATION AND non motor symptoms of PARKINSON

Cognition: Open Field, + Maze, Forced Swimming, Sucrose Consumption
Circadian Behavior: Actimetry (CAMS) for locomotor activity
Electrophysiology, Monoamines Assays

✓ Rats aged 4 to 6 weeks
   - Controles (Sodium Acetate, i.p, 10mg/Kg, n=10)
   - Treated (Lead Acetate, i.p, 10mg/kg, n=24)
- Body Weight
- Cognitive Functions
- Humour: Anxiety & Depression
- Motor Coordination
- Circadian Rhythms
Body Weight
- Exploratory Behavior
Humeur: Anxiété et dépression
Motor Coordination
Circadian Rhythms

Exploratory Behavior

Locomotor Activity

Open Field Test

20 min
Body Weight
Cognitive Function
• Humeur: Anxiety & Depression dépression
Motor Coordination
Circadian Rhythms

Elevated Plus Maze

![Graphs showing time spent in open arms and entries in open arms between control and lead conditions.](image-url)
Body Weight
Cognitive Function
- Humeur: Anxiety & Depression
Motor Coordination
Circadian Rhythms

Sucrose Consumption

\[
100 \times \left[ \frac{\text{sucrose intake (g)}}{\text{sucrose intake (g)} + \text{water intake (g)}} \right]
\]
Body Weight
Cognitive Function
Humeur: Anxiety & Depression
- Motor Coordination
Circadian Rhythms
Body Weight
Cognitive Function
Humeur: Anxiety & Depression
Motor Coordination
• Circadian Rhythms
Body Weight
Cognitive Function
Humeur: Anxiety & Depression
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Body Weight
Cognitive Function
Humeur: Anxiety & Depression
Motor Coordination
• Circadian Rhythms
Body Weight
Cognitive Function
Humeur: Anxiety & Depression
Motor Coordination
• Circadian Rhythms

Entrainement by Light

Light off: 6:00pm

Light off: 12:00
Body Weight
Cognitive Function
Humeur: Anxiety & Depression
Motor Coordination
• Circadian Rhythms

Moyenne des cellules ir-FOS

Contrôles Traités
0
50
100
150
200
250
*

Contrôle
Lead

Light
**Contrôles**

**Traités**

**Moyenne des cellules ir-VP**

![Graph showing the comparison between Contrôles and Traités for ir-VP](image)

**Vasopressine**

**Contrôle**

**Traité**

**Moyenne des cellules ir-VIP**

![Graph showing the comparison between Contrôles and Traités for ir-VIP](image)

**VIP**

**Contrôle**

**Traité**

**Body Weight**

**Cognitive Function**

**Humeur: Anxiety & Depression**

**Motor Coordination**

- **Circadian Rhythms**
Body Weight
Cognitive Function
Humeur: Anxiety & Depression
Motor Coordination
• Circadian Rhythms

GFAP: Astrocytes

Moyenne des cellules ir-GFAP

Contrôles
Traités

Contrôles
Traités

*
Contrôles et Traités

Moyenne des cellules

Ir-BMAL1

Ir-PER1

Ir-PER2

CLOCK PROTEIN EXPRESSION

Body Weight
Cognitive Function
Humeur: Anxiety & Depression
Motor Coordination
• Circadian Rhythms
CONCLUSION

• Lead induces functional disorders that resemble those find in Parkinson’s like disease patients or Parkinson’s disease classical animal models.

• Disturbancy in cognitive functions, behavior, houmur, circadian rhythms (sleep Wake cycle?)

• Lead induces also a loss in SCN neurones and astrocytes: degenerative processes by necrosis or death?

• It can be responsible for Parkinsonism symptome

• The correlation to idiopathic form of Parkinson’s remains to be determined
Manganese-induced atypical parkinsonism is associated with altered Basal Ganglia activity and changes in tissue levels of monoamines in the rat.


Lead intoxication induces noradrenaline depletion, motor nonmotor disabilities, and changes in the firing pattern of subthalamic nucleus neurons.

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cMIRA Rhone-Alpes
(France)-Rabat Salé
(Morocco) Convention

GDRI Neuro
French-Morocco Network

Neuromed « Building Capacities in Mediterranean Area
Thank You