Social stressors and suicidal behaviour: neurobiology

Philippe Courtet
Montpellier
(Organisation Mondiale de la Santé)

WHO estimates about 1.5 million deaths by suicide per year worldwide by 2020

10-20 fold more suicide attempts

Stress associés aux Conduites Suicidaires

“Raisons” de Conduites Suicidaires

- Dépression
- Schizophrénies
- Alcoolisme
- Personnalité

Troubles Psychiatriques

- Autres
- Stress associés aux

K. Menninger
Man against Himself (1938):
"Unconscious purposes are more significant in understanding suicide than apparently simple, inevitable, external circumstances"

Suominen et al Am J Psychiatry 2004

L’histoire de TS est un indicateur de la vulnérabilité

100 suicides
13% suicides à 37 ans:
- 8% chez les femmes
- 26% chez les hommes

Les 2/3 des suicides surviennent après 15 ans

Moyens de suicide:
- 62% surdoses médicamenteuses
- 31% pendaisons
- 8% sauts

Need of biomarkers

- "Biomarkers related to the diathesis might help to refine risk-assessment procedures and treatment choice in the prevention of suicide" (van Heeringen & Mann Lancet Psychiatry 2014)

Psychiatric biomarker should:
- detect a discrete characteristic related to a disorder, its severity or treatment efficacy
- be safe and easy to measure peripherally
- have sensitivity >80% for detection and specificity >80% for differentiation from similar traits
- be reliable and reproducible to allow standardization between labs
- be inexpensive,
Biochemical markers that may predict prospectively high-lethality attempts (less clear than for suicides)

- Low CSF levels of 5-HIAA
  - OR = 4.48
- Non-suppression DST
  - OR = 4.65

Independent biological risk factors:
- Mann & Currier Archives of Suicide Research 2007
- Jokinen Psychiatry Res 2009

The possibility of Inflammation in suicidal behaviour

- Suicide risk is elevated among patients being treated with cytokines for medical problems (proliferative, hepatitis C, HIV infections, and multiple sclerosis).
- Epidemiological studies have revealed an association between suicidal ideation and behaviour and allergy, asthma and T. Gondii.
- Procedures such as faecal transplants can reduce the risk of suicidal ideation and behaviour.

Cytokines levels in the brains of suicide victims

<table>
<thead>
<tr>
<th>Study/Male et al. 2014</th>
<th>34 depressed suicides: no difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandey et al. 2012</td>
<td>26 suicide victims (versus controls)</td>
</tr>
<tr>
<td></td>
<td>24 control cards (versus controls)</td>
</tr>
<tr>
<td>Towell et al. 2008</td>
<td>34 suicide victims (diagnosis)</td>
</tr>
<tr>
<td></td>
<td>34 non-suicide control cases</td>
</tr>
<tr>
<td>Steiner et al. 2008</td>
<td>34 suicide victims (diagnosis)</td>
</tr>
<tr>
<td></td>
<td>34 matched norm. controls</td>
</tr>
</tbody>
</table>

Microglia activation in the brains of suicide victims

- Greater density of activated microglia in the dorsal raphe nucleus, anterior cingulate cortex, and ventromedial thalamus.
- Increased expression of inflammatory cytokines (IL-1β, IL-6, TNF-α).
- Higher proportion of blood vessels surrounded by a high density of microglia.

A meta-analysis of cytokines in suicidal behavior

Increased CRP levels may be a trait marker of suicidal attempt

Inflammation contributes to the pathophysiology of suicidal behavior

Ketamine: anti-suicidal & anti-inflammatory?

Genetics of suicide

"5-HTTLPR-SS" associated with suicidal recurrence
Genes of stress in suicidal behaviour

- Low CSF 5HIAA and DST non-suppression are orthogonal biological risk factors for suicide

ACE polymorphisms in converting enzyme gene CRH-R1: association & linkage to suicide attempts in depressed males exposed to low levels of stress


Low CSF 5-HIAA and DST non-suppression are orthogonal biological risk factors for suicide

Gene x Environment


Childhood Abuse, Household Dysfunction, and the Risk of Attempted Suicide Throughout the Life Span: Findings From the Adverse Childhood Experiences Study (Dubé et al JAMA 2001)

Risk of T S / adolescent > risk of T S at age adult

From Childhood abuse to suicidal behaviour

SB Early onset SB

Les conséquences biologiques du harcèlement

Methylation gene transporter SERT 50 pairs children MEZ discordant (harcèlement)

Effet (épigénétique) à long terme des stress & des antidépresseurs

La régulation épigénétique du récepteur aux glucocorticoides dans le cerveau humain est sensible aux stress de l'enfance

Weaver et al 2004, McGowan et al 2009

La régulation épigénétique du récepteur aux glucocorticoides dans le cerveau humain est sensible aux stress de l'enfance

Weaver et al 2004, McGowan et al 2009

Méthylations gène transporteur 5HT 50 paires jumeaux MEZ discordants (harcèlement)

CRP ph ènotype prévalence en population, n = 1,400, suivi durant 3,39 ans

Les conséquences biologiques du harcèlement
Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma

- NMDA Subthreshold personality disorder (high rate of childhood maltreatment)
- NMDA MDD (low rate of childhood maltreatment)
- NMDA MDD + PTSD

Identification and Replication of a Combined Epigenetic and Genetic Biomarker Predicting Suicide and Suicidal Behaviors

SKA2 Gene As Epigenetic Biomarker of Suicide or Suicidal Behavior

Mann et al Arch Gen Psychiatry 2000; 57: 729-738

5-HTT

Jollant et al Am J Psychiatry 2005

Decision Making Impairment is a cognitive trait of vulnerability to SB

Neural Bases of Decision Making Impairment

Males
- History of Depression & Euphoria
  - 13 SA+
  - 6 SA-
- 16 healthy controls

Jollant et al Neurimage 2010
Neuroanatomy of suicide attempts: sensitivity to social rejection / social support

Olie et al. 2015
Neuroanatomy of suicide attempts
Higher sensitivity to social rejection decreases sensitivity to social support
precedes to feel psychological pain
prefer solutions with immediate high reward even if deleterious

Social exclusion - psychological pain - suicide

Social adversity
- Separation
- Conflict with the spouse
- Other relational problems
- Social problems
- Diseases (physical or mental)

Social Exclusion

Psychological pain

Kross et al. PNAS 2011
Painkillers and suicidal vulnerability
- 857 subjects over 65 years old, community dwelling
- 41 subjects with a lifetime history of suicide attempts vs 410 affective controls and 406 healthy subjects
- Exhaustive prescription during 3 years follow up
- Opioid analgesic consumption associated with a 2.35 times
  increased risk (adjusted for gender, age, education, chronic diseases, hospitalization, living alone, subjective health & exclusion of cancer cases)
- Further analysis in a partially overlapping sample (n=858)
  - Suicidal patients: higher rate of opioid prescriptions
  - Non-suicidal patients: higher rates of pain
  - Suicidal patients: higher impact of pain on quality of life

Social, physical, psychological pains: all present in suicidal behaviour

The impact of physical pain on suicidal thoughts and behaviors: Meta-analysis
Raffaella Colato, Poy G., Philo C., Camillo Laghetti M.P., Philo D., Sylvain Antes, Philo D., Marco Spena, Philo D., Philippe Courter, MD, Philo D. 2015

Painkillers and suicidal vulnerability
- 857 subjects over 65 years old, community dwelling
- 41 subjects with a lifetime history of suicide attempts vs 410 affective controls and 406 healthy subjects
- Exhaustive prescription during 3 years follow up
- Opioid analgesic consumption associated with a 2.35 times
  increased risk (adjusted for gender, age, education, chronic diseases, hospitalization, living alone, subjective health & exclusion of cancer cases)
- Further analysis in a partially overlapping sample (n=858)
  - Suicidal patients: higher rate of opioid prescriptions
  - Non-suicidal patients: higher rates of pain
  - Suicidal patients: higher impact of pain on quality of life
μ-opioid receptor (OPRM1)

Social pain (rejection / exclusion)

Suicide

Social rejection is associated with inflammatory responses to social stress

Slavich et al. PNAS 2010

Buprenorphine ultra-low dose for treating serious suicidal ideation

- RCT double blind, buprenorphine sublingual: 0.44 mg/d, n=40 vs placebo, n=22, in addition
- High risk patients: suicidal ideation, suicide attempt in 66.3%
- Without substance misuse
- Main objective: suicidal ideation at 4 weeks

Yowell et al. AJP 2016

Acute social stressors

Yowell et al. AJP 2016