Schizophrénie et stress oxydatif : des hypothèses longtemps contradictoires, enfin réconciliées? Perspectives cliniques

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Conflits d'intérêt

- L'auteur déclare avoir eu des activités de conseil, participé à des manifestations pour les laboratoires :
  - Otsuka
  - Janssen-Cillag

- Aucun en lien avec cette présentation

Le centre hospitalier Guillaume Régnier

- EPSM de Rennes
- 1747 lits et places (en 2015)

Carte Sectorielle départementale Adulte

Carte Sectorielle départementale Enfant

« There is certainly a risk in predicting scientific progress. The most important discoveries will probably be ones we cannot imagine today. »

Thomas R. Insel, Nature 2010

« [.] existing diagnostic categories might not be the best for stratification of cases for research into disease cause and pathogenesis. »

« [.] schizophrenia might be best conceived as one of a spectrum of clinical outcomes that result from disruption to the developing brain induced by genetic or environemental factors, or both. »

Owen et *al.*, Lancet 2016

« La ké c'est trop une drogue de fou, ça me fait flipper, je me met a parler a mes meubles et devant mon pc devant un divx, j'ai l'impression d'être dans le film… je perd toute notion de la réalité… enfin quelle réalité ?? »

Queb 69, Psychoactif 2018

La question : « ? »

Schizophrenia Research

Volume 159, Issues 2–3, November 2014, Pages 411–414

Use of very-high-dose olanzapine in treatment-resistant schizophrenia

J.-M. Batail[a, b], B. Langrée[c, e, f], G. Robert[a, b], S. Bleher[a, b], M.-C. Verdier[d, e, f], E. Bellissant[d, e, f], B. Millet[a, b], D. Drapier[a, b]

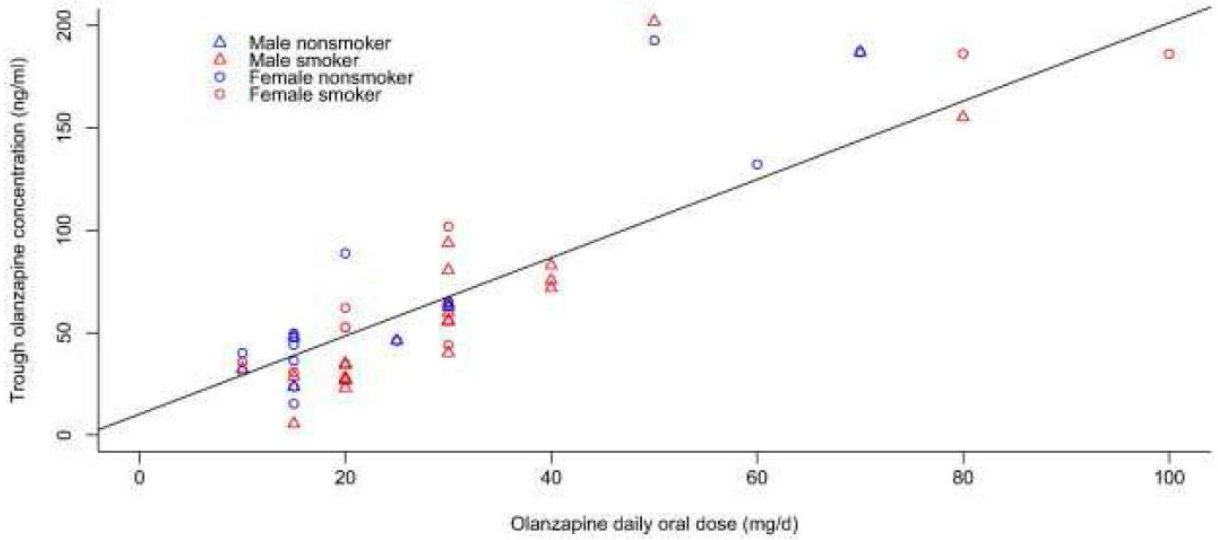


Fig. 1. Relationship between trough olanzapine concentration and daily oral dose of olanzapine.

Le stress oxydatif

Le stress oxydatif

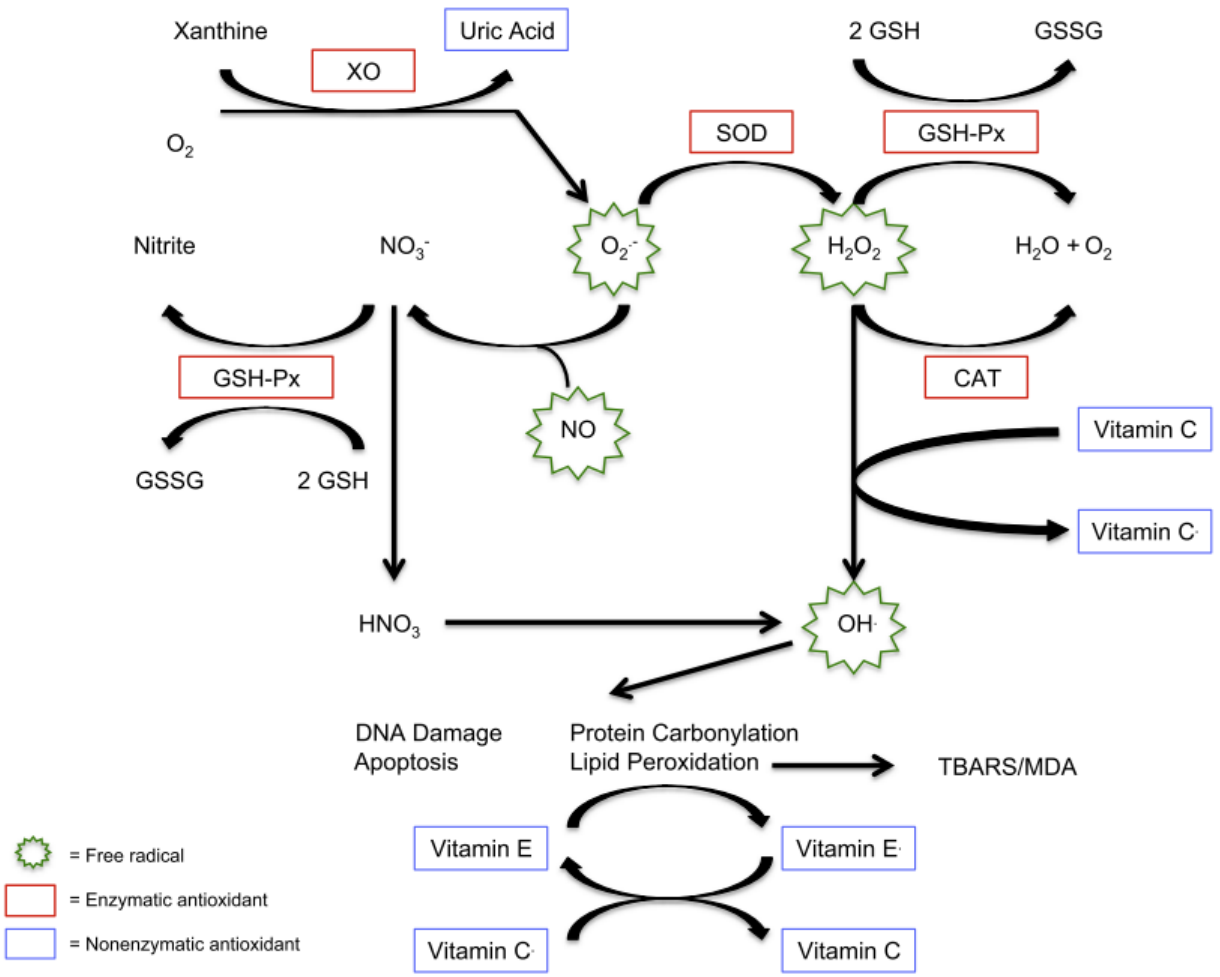


Figure 1. Potential relationships between free radicals and antioxidant defenses. Superoxide dismutase (SOD) catalyzes the conversion of superoxide radicals (O_2–) to hydrogen peroxide (H_2O_2). Both catalase (CAT) and glutathione peroxidase (GSH-Px) convert H_2O_2 to water (H_2O) and oxygen (O_2). Reduced glutathione (GSH) is oxidized by GSH-Px to oxidized glutathione (GSSG). The GSH-Px also converts nitrate (NO_3–, a by-product of nitric oxide radicals) to nitrite. Nitrite is often used as a marker for nitric oxide (NO) activity. Hydroxyl radicals (OH.), which are produced from both H_2O_2 and NO, promote apoptosis, DNA damage, protein carbonylation, and lipid peroxidation. Thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) are important end products of lipid peroxidation. The TBARS measures endogenous MDA, although additional MDA might be generated in the assay.

Les origines

- Fin des années 1980 :
  - Fortes corrélations entre les marqueurs du stress oxydatif et la maladie
  - Pas de causalité
  - Beaucoup d'études contradictoires

Table 1
Studies on oxidative stress in schizophrenia, bipolar disorder and major depression.

Antioxidant	Decreased biomarker	Increased biomarker
Schizophrenia		
Superoxide Dismutase (SOD)	Mukerjee et al. (1996); Akyol et al. (2002); Ranjekar et al. (2003); Dietrich-Muszalska et al. (2005); Li et al. (2006); Zhang et al. (2006); Zhang et al. (2007); Ben Othmen et al. (2008)	Abdalla et al. (1986), Kuloglu et al. (2002); Michel et al. (2004)
Glutathione Peroxidase (GPx)	Abdalla et al. (1986), Ben Othmen et al. (2008); Li et al. (2006); Ranjekar et al. (2003); Yao et al. (2006); Zhang et al. (2006); Zhang et al. (2007); Gawryluk et al. (2011)	Kuloglu et al. (2002)
Catalase (CAT)	Ranjekar et al. (2003); Li et al. (2006); Zhang et al. (2006); Zhang et al. (2007); Ben Othmen et al. (2008)	
Glutathione (GSH)	Altuntas et al. (2000), Yao et al. (2006); Dietrich-Muszalska et al. (2009); Do et al. (2000)	
Thiobarbituric acid related substances (TBARS)		Akyol et al. (2002); Khan et al. (2002); Kuloglu et al. (2002); Ranjekar et al. (2003); Dietrich-Muszalska et al. (2005); Zhang et al. (2006); Zhang et al. (2007); Ben Othmen et al. (2008)
Lipid peroxide		Li et al. (2006)
Homocysteine		Akanji et al. (2007); Dietrich-Muszalska et al. (2009)
Nitric Oxide (NO)		Akyol et al. (2002); Yanik et al. (2003); Li et al. (2006); Yilmaz et al. (2007)

C.D. Pandya et al. / Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (2013) 214–223

Les origines

- Déception quand on passe à la phase traitement :

Table 2
Adjunctive antioxidant therapy in neuropsychiatric disorders.

	Treatment	Trial type	Findings	Reference
Schizophrenia				
Vitamins	Vitamins E, C (400 IU:500 mg) along with EPA/DHA	Adjunct therapy for 4 months	Decrease in BPRS and PANSS	Arvindakshan et al. (2003)
	Vitamin C (500 mg/day) with atypical antipsychotics	8 week, double-blind, placebo-controlled, noncrossover trial	Decrease in BPRS and oxidative stress Increase in ascorbic acid levels	Dakhale et al. (2005)
N-acetyl-cysteine (NAC)	2 g/day	60 day, double-blind, randomized, placebo-controlled trial	EEG synchronization	Carmeli et al. (2012)
	1 g orally twice daily	24 week, randomized, multicenter, double-blind, placebo-controlled study	Improved in PANSS total, PANSS negative, PANSS general, CGI-Severity, and CGI-Improvement scores	Berk et al. (2008)
ethyl eicosapentaenoic acid (EPA)	3 g/day	16-week, double-blind supplementation	No change in symptoms	Fenton et al. (2001)
	1, 2 or 4 g/day	Adjunct therapy for 12 weeks	Improvements in PANSS at 2 g/day	Peet and Horrobin (2002)
	EPA/DHA (180:120 mg) along with vitamins	Adjunct therapy for 4 months	Clinical significance of improvement remained after EPUFAs normalized to baseline with washout.	Arvindakshan et al. (2003)
	2 g/day	12-week, randomized, double-blind, placebo-controlled trial	No change in symptoms	Berger et al. (2007)

C.D. Pandya et al. / Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (2013) 214–223

Puis : notion de staging

50% des jumeaux homozygotes sont atteints

Chez la mère : malnutrition, infection
Chez le fœtus : exposition aux cytokines, lésion périnatale

Early intervention

Table 1 | Stages of schizophrenia

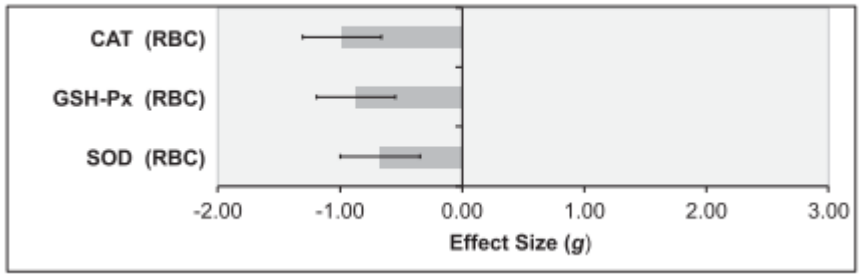
	Stage I	Stage II	Stage III	Stage IV
Features	Genetic vulnerability Environmental exposure	Cognitive, behavioural and social deficits Help-seeking	Abnormal thought and behaviour Relapsing–remitting course	Loss of function Medical complications Incarceration
Diagnosis	Genetic sequence Family history	SIPS Cognitive assessment Imaging	Clinical interview Loss of insight	Clinical interview Loss of function
Disability	None/mild cognitive deficit	Change in school and social function	Acute loss of function Acute family distress	Chronic disability Unemployment Homelessness
Intervention	Unknown	Cognitive training? Polyunsaturated fatty acids? Family support?	Medication Psychosocial interventions	Medication Psychosocial interventions Rehabilitation services

Stage I, pre-symptomatic risk; stage II, pre-psychotic prodrome; stage III, acute psychosis; stage IV, chronic illness.

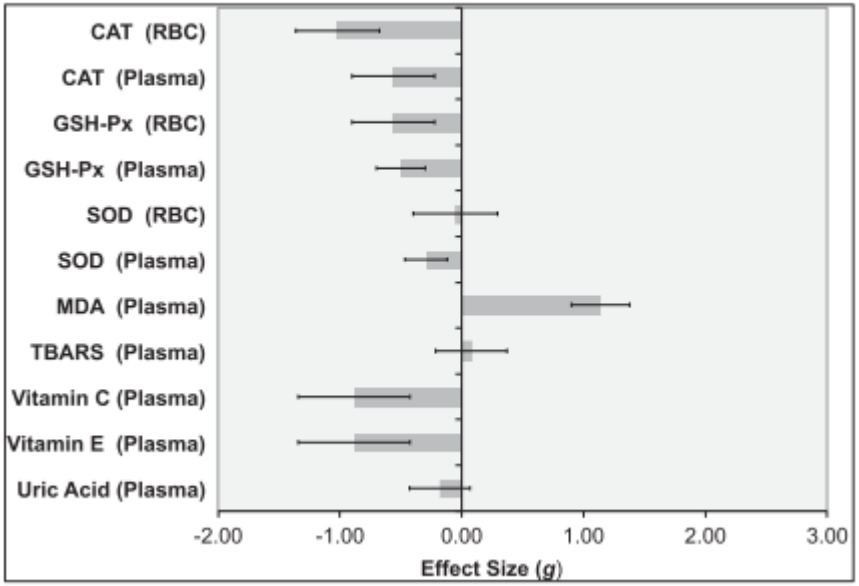
Insel, T.R., 2010. Rethinking schizophrenia. Nature 468, 187–193. doi:10.1038/nature09552

Puis notion de staging

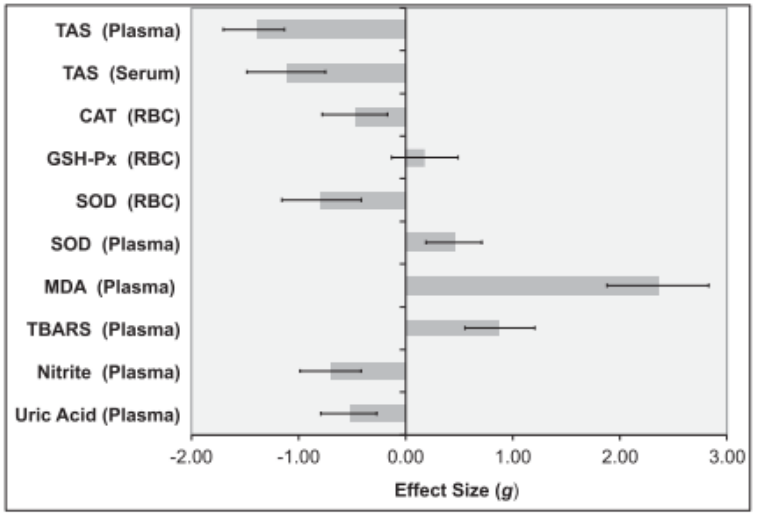
A. Acute Relapse



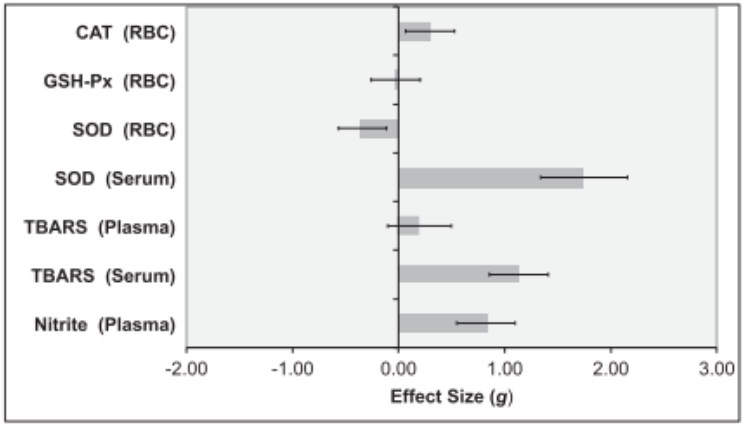
F. Chronic Inpatient



C. First-Episode Psychosis



D. Stable Outpatient



Flatow *et al.* 2013

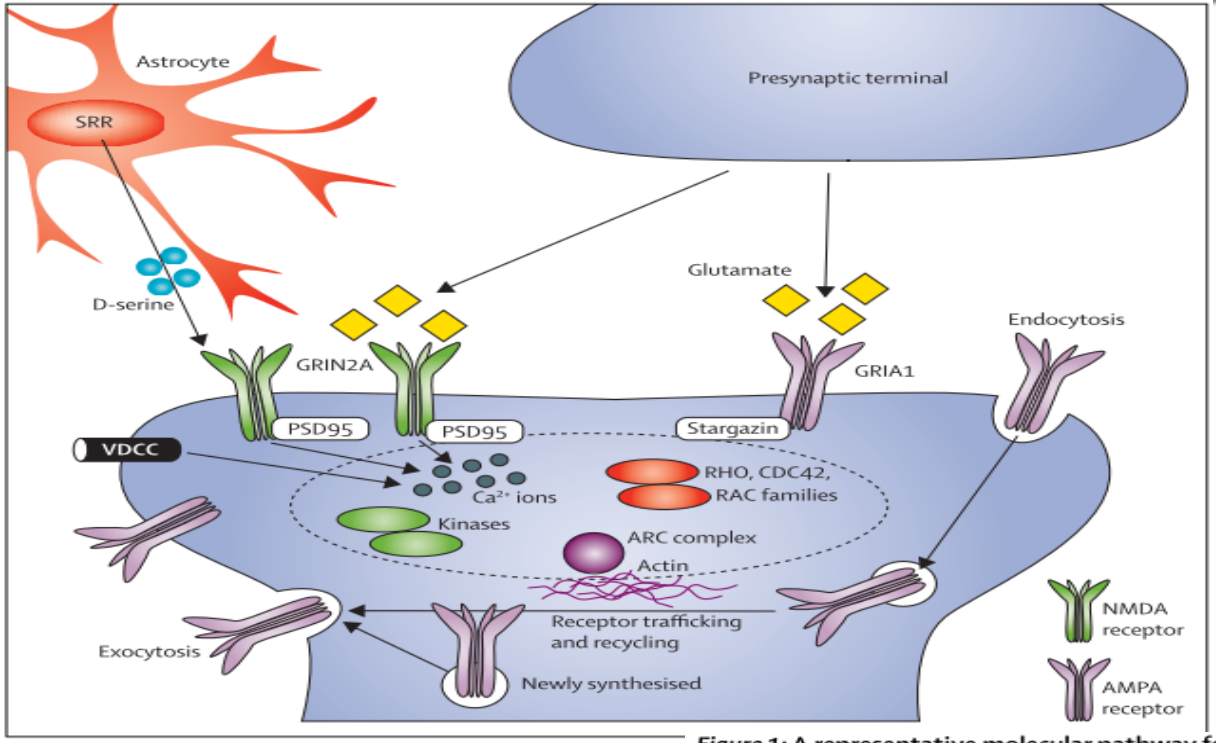
Un regain d'intérêt

On se concentre sur les interneurones

- Multiples modèles animaux de schizophrénie:
  - NVHL rats (neonatal ventral hipoccampal lesion)
  - Injections néonatales de LPS
  - Traitement prénatal à l'acétate de methylazoxymethanol (antimitotique)
  - DISC1 ko, dysbindin ko
  - Etc.
  - 1 effecteur commun :

Parvalbumin interneurone

Hypothèse du stress oxydant



Schizophrenia

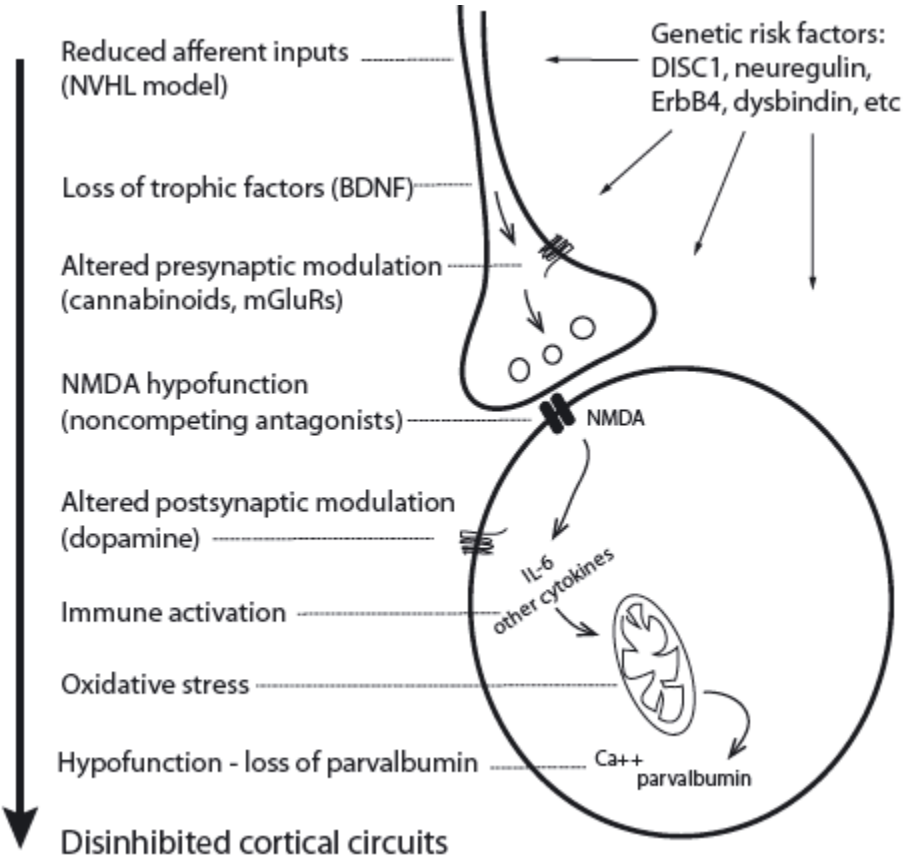
Michael J Owen, Akira Sawa, Preben B Mortensen

The Lancet

http://dx.doi.org/10.1016/S0140-6736(15)01121-6

Figure 1: **A representative molecular pathway for schizophrenia—fine-tuning of the glutamate synapse**
Advances in human genetics, from both genome-wide association studies and large-scale sequencing, have lent further support to the importance of fine-tuning of glutamatergic neurotransmission in the pathology of schizophrenia. The genes implicated in these studies include *GRIN2A* (which encodes a subunit of the NMDA receptor), *GRIA1* (which encodes a subunit of the AMPA receptor), *SRR*, *CACNA1C*, genes encoding the ARC complex, and several genes encoding proteins located in, or associated with, the post-synaptic density of glutamatergic synapses. The NMDA-type glutamate receptors are fine-tuned by the co-agonist D-serine, which is synthesised by SRR. VDCCs (eg, the protein encoded by *CACNA1C*) are also likely to be involved in tuning neural excitability and synaptic transmission via intracellular calcium signalling. In response to activation of glutamate receptors, proteins associated with the post-synaptic scaffold—eg, PSD95, stargazin (also known as CACNG2), several kinases, the RHO, CDC42, and RAC family of small G proteins, and the ARC complex—convey intracellular signalling that underlies cytoskeletal regulation and receptor trafficking, which are crucial for synaptic plasticity. The dashed oval represents converged intracellular protein networks that underlie synaptic plasticity. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid. NMDA=N-methyl-D-aspartate. PSD=post-synaptic density protein. SRR=serine racemase. VDCC=voltage-dependent calcium channel.

Hypothèse du stress oxydant



European Journal of Neuroscience, Vol. 35, pp. 1866–1870, 2012 doi:10.1111/j.1460-9568.2012.08130.x

Cortical interneurons, immune factors and oxidative stress as early targets for schizophrenia

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FIG. 1. Cartoon illustrating a cortical interneuron and a representative glutamatergic afferent indicating where vulnerability factors can affect interneuron function during development, and possible events occurring in animal models that ultimately yield disinhibited cortical circuits. A reduction in NMDA receptor function in GABAergic interneurons could be driven by NMDA antagonists, reduced inputs, reduced trophic factors, etc. Reduced NMDA activation in this cell population induces cytokine expression and redox alterations, and eventually lower levels of PV. PV is a calcium-buffering protein that may not be needed if neurons are hypoactive; therefore, PV loss may not indicate cell death, but lack of sufficient activity. Genetic risk factors may contribute to this scenario both at the pre- and post-synaptic level. BDNF, brain-derived neurotrophic factor. Reproduced from O'Donnell (2011), with permission.

Hypothèse du stress oxydant

- Mais depuis 2010 le rôle du stress oxydant dans la schizophrénie s'affine

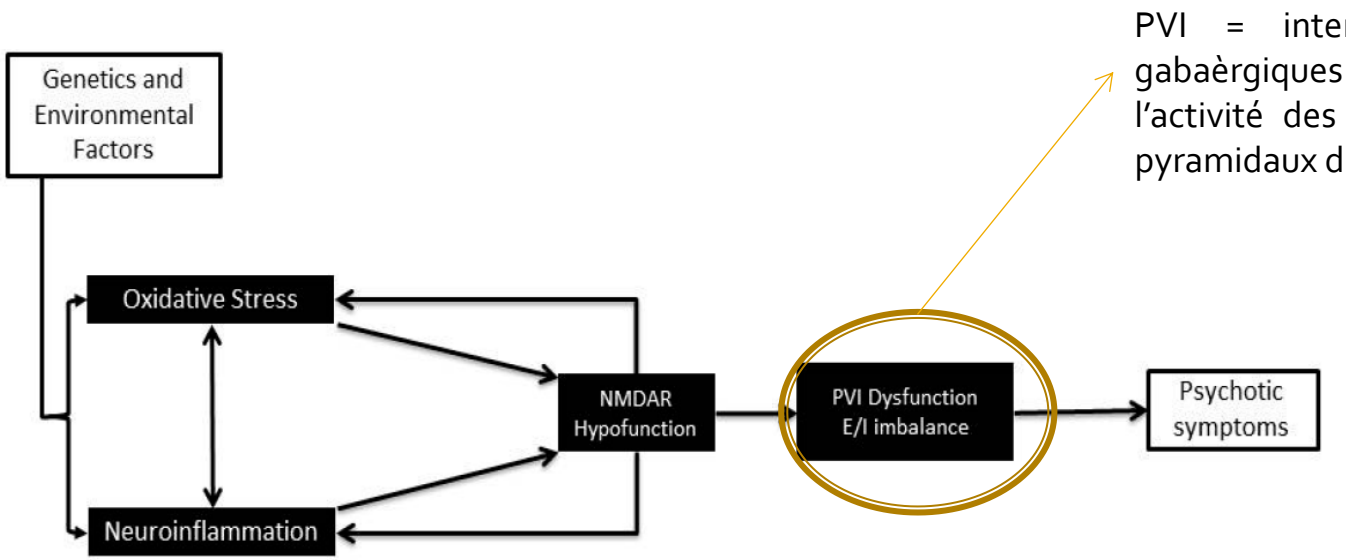
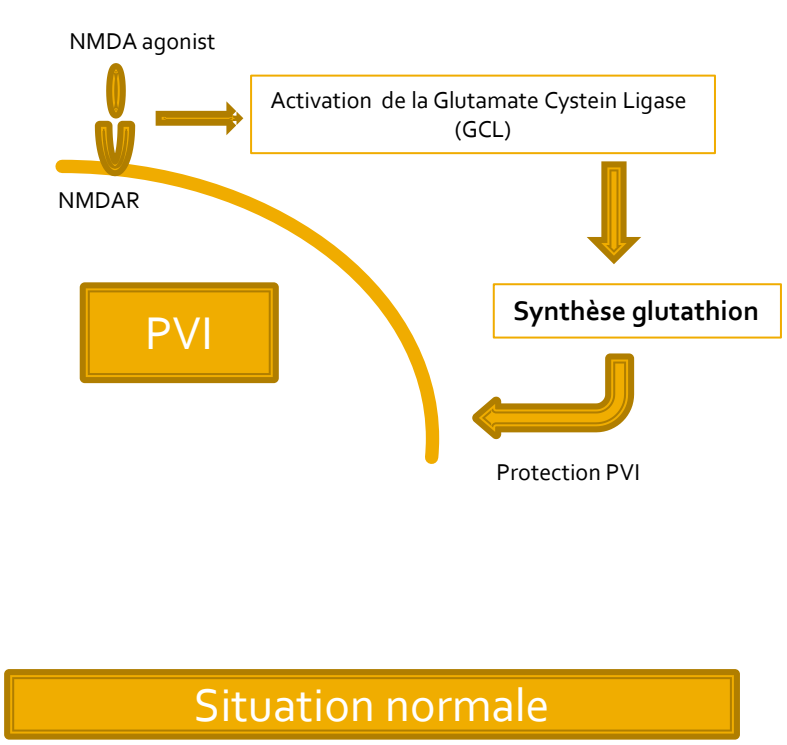
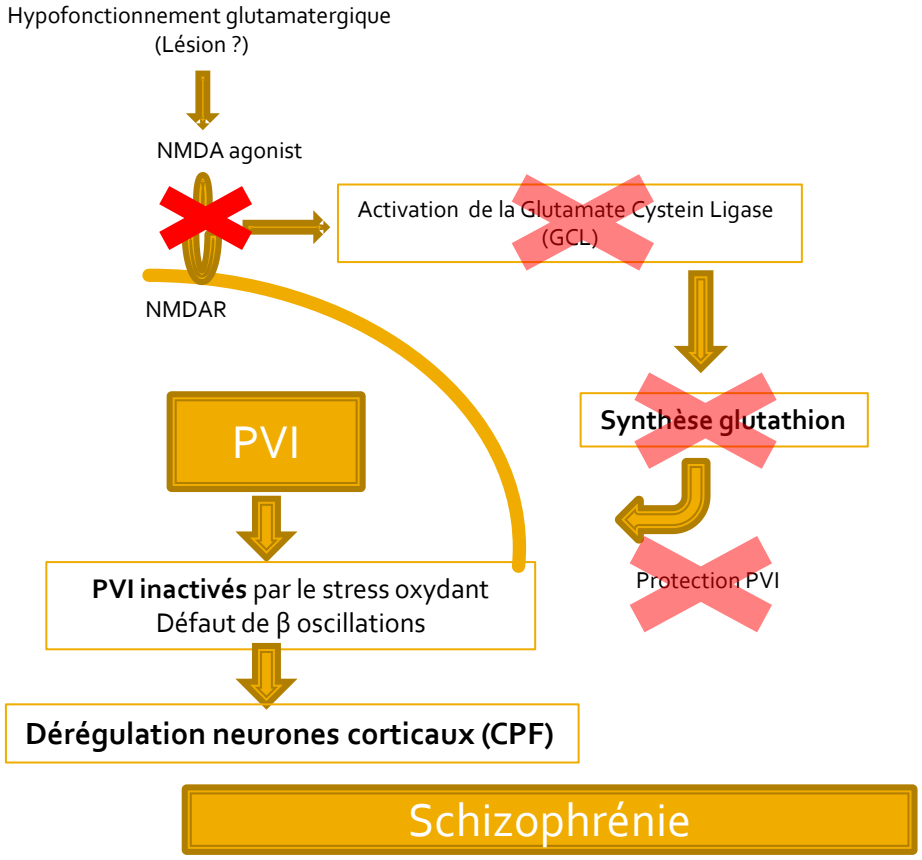


Figure 1. A simplified model of the link between neuroinflammation, oxidative stress and psychosis.

Barron *et al.* *Int. J. Mol. Sci.* **2017**, *18*, 651; doi:10.3390/ijms18030651

Hypothèse du stress oxydant





Hypothèse sur l'implication du stress oxydant dans la schizophrénie

Hypothèse du stress oxydant

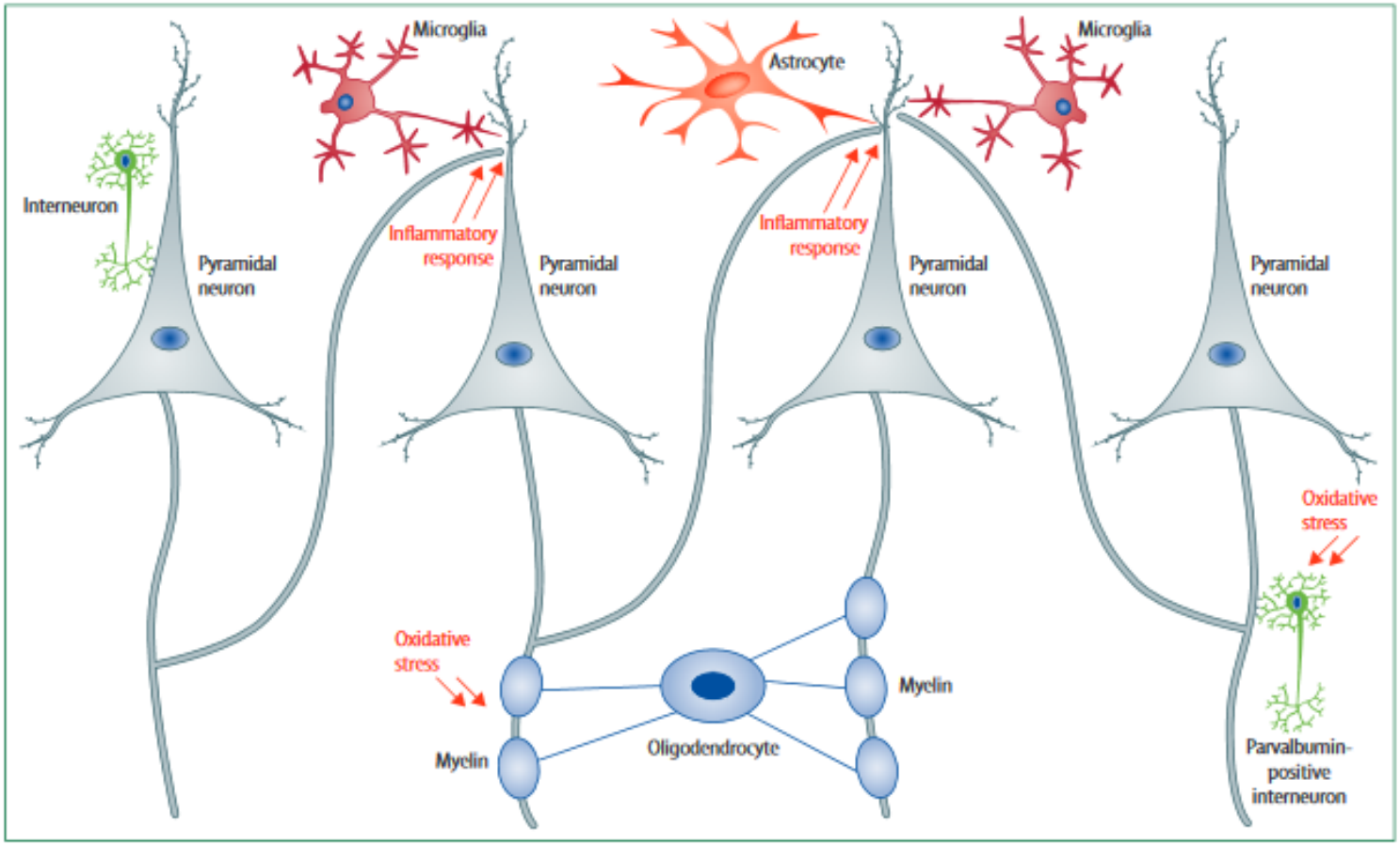


Figure 3: **Neuron–glia interactions in the cerebral cortex—key neural substrates for the pathology of schizophrenia**
In the cerebral cortex, interneurons (inhibitory neurons) regulate the output of pyramidal neurons (excitatory neurons). Many studies have reported abnormalities of interneurons (particularly parvalbumin-positive interneurons) and deficits of dendritic spines in the pyramidal neurons in schizophrenia. Imbalance of excitatory and inhibitory neurons might be a key feature that underlies disease pathology. Parvalbumin-positive interneurons are particularly vulnerable to oxidative stress, reflecting an imbalance between the production of reactive oxygen species and the availability of antioxidants, which leads to cellular damage. Astrocytes and microglia have key roles in the maintenance and pruning of dendritic spines, which involves immune inflammatory mechanisms. Oligodendrocytes create the myelin sheath, which is crucial for signal transmission inside the axon. Abnormalities of these glial cells have also been reported in schizophrenia.

Ce qu'il se passe alors…

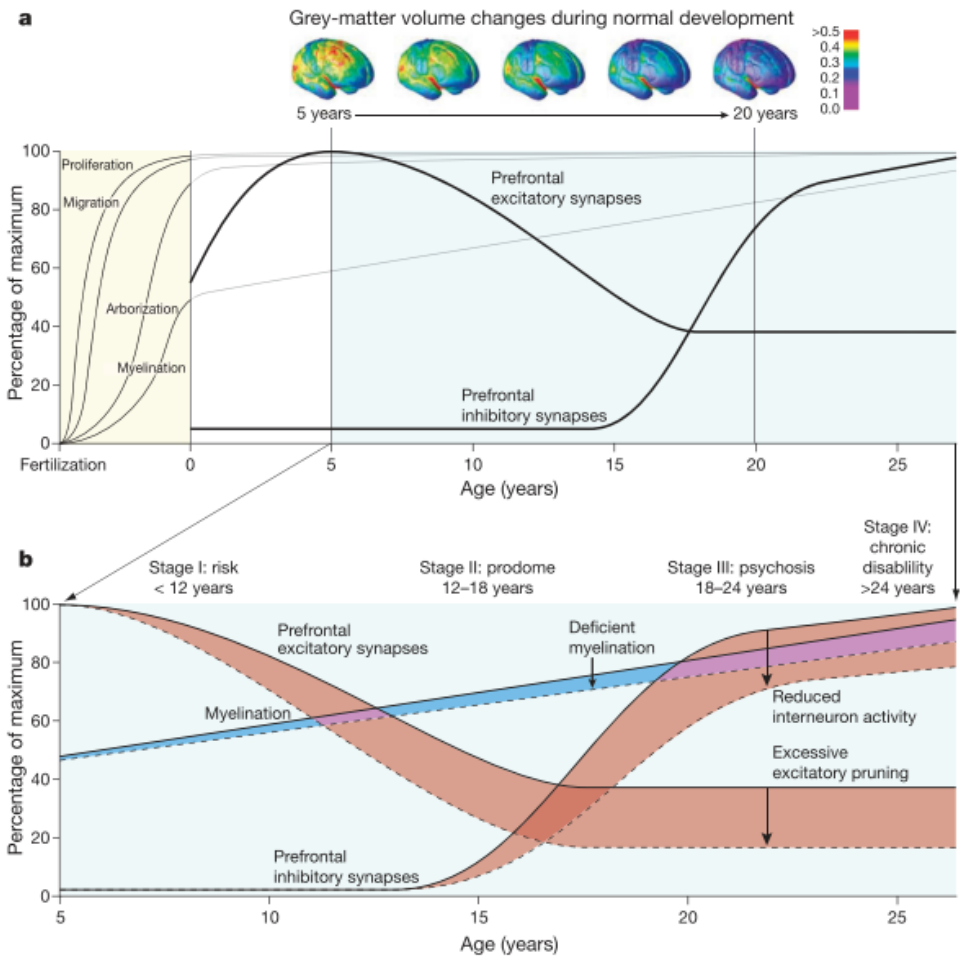


Figure 1 | Neurodevelopmental model of schizophrenia. **a**, Normal cortical development involves proliferation, migration, arborization (circuit formation) and myelination, with the first two processes occurring mostly during prenatal life and the latter two continuing through the first two post-natal decades. The combined effects of pruning of the neuronal arbor and myelin deposition are thought to account for the progressive reduction of grey-matter volume observed with longitudinal neuroimaging. Beneath this observed overall reduction, local changes are far more complex. Data from human and non-human primate brain indicate increases in inhibitory and decreases in excitatory synaptic strength occurring in prefrontal cortex throughout adolescence and early adulthood, during the period of prodrome and emergence of psychosis. **b**, The trajectory in children developing schizophrenia could include reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways leading to altered excitatory–inhibitory balance in the prefrontal cortex. Reduced myelination would alter connectivity. Although some data support each of these possible neurodevelopmental mechanisms for schizophrenia, none has been proven to cause the syndrome. Detection of prodromal neurodevelopmental changes could permit early intervention with potential prevention or preemption of psychosis.

Insel, T.R., 2010. Rethinking schizophrenia. Nature 468, 187–193. doi:10.1038/nature09552

Perspectives cliniques?

Neuroscience Research 69 (2011) 283–290

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Protective effects of atypical antipsychotic drugs against MPP^+-induced oxidative stress in PC12 cells

Sung Woo Park[a], Chan Hong Lee[a], Jung Goo Lee[a,c,d], Luck Woo Kim[c], Bae Sub Shin[c], Bong Ju Lee[c,d], Young Hoon Kim[a,b,c,d,*]

L'olanzapine semble bien protecteur
Mécanisme?

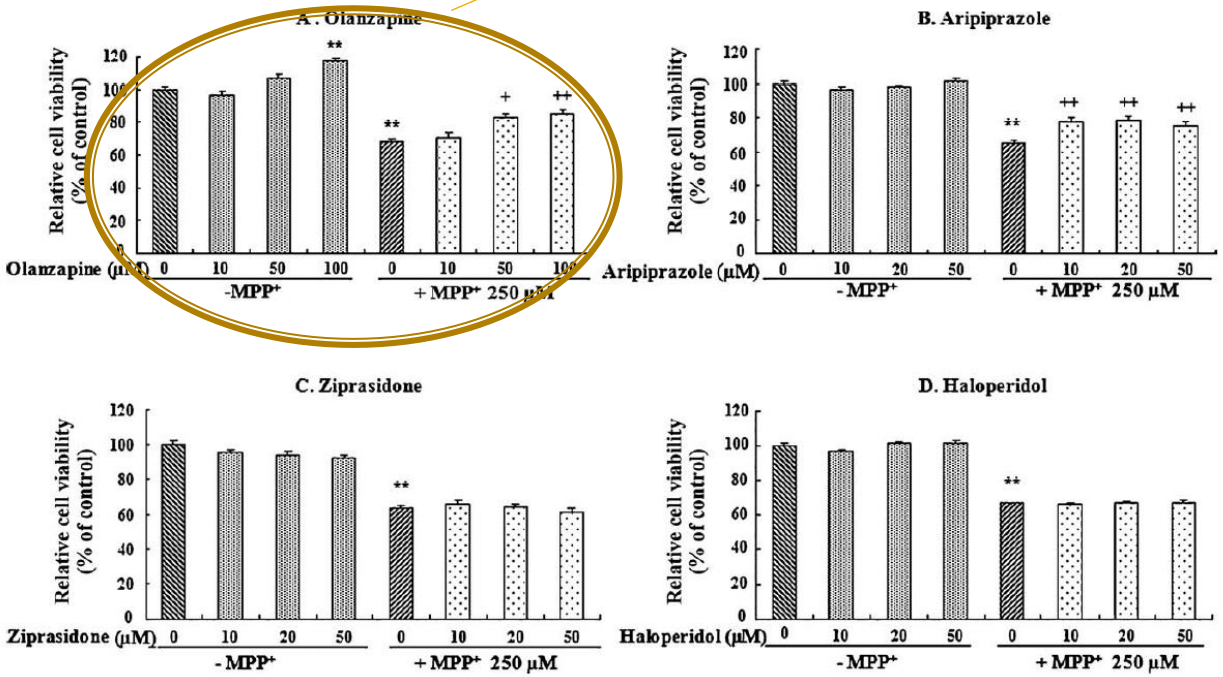


Fig. 1. Effects of antipsychotic drugs on the cell viability in PC12 cells. Cells were treated with different doses of antipsychotic drugs for 48 h with (+MPP^+) or without (−MPP^+) 250 μM MPP^+, after which the MTT assay was performed. (A) Olanzapine; (B) aripiprazole; (C) ziprasidone; (D) haloperidol. Values are expressed as a percentage of the control value (−MPP^+, no drug treatment) and represent means ± S.E.M. from the three independent experiments. $^{**}p < 0.01$ vs. untreated control; $^{+}p < 0.05$ vs. MPP^+ treated only, $^{++}p < 0.01$ vs. MPP^+ treated only.

Perspectives cliniques?

- Avec la quétiapine : capture radicalaire

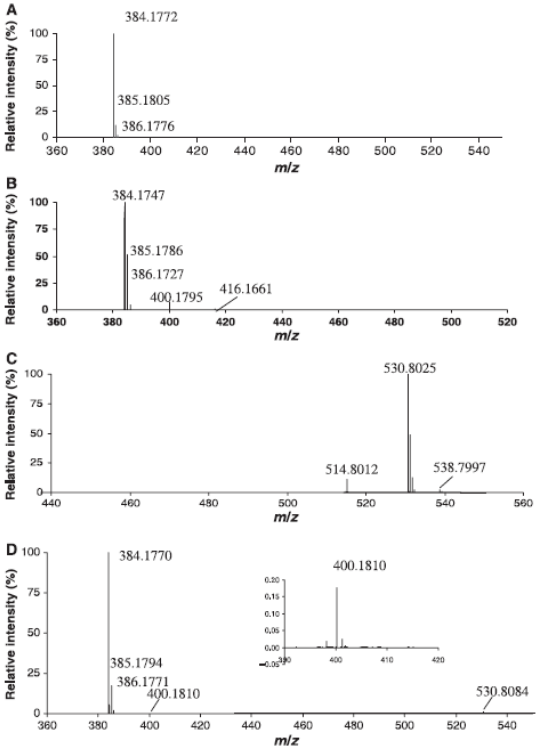


Fig. 5. Quetiapine captures hydroxyl radicals. Mass spectra were obtained from the following cell-free aqueous solutions: (A) 100 μM quetiapine, (B) the Fenton reaction solution mixed with 100 μM quetiapine, (C) 1 mM Aβ(25-35) and (D) 1 mM Aβ(25-35) mixed with 1 mM quetiapine. Before obtaining the mass spectra, solutions A and B were incubated at 22 °C for 2 h, and solutions C and D were incubated at 37 °C for 24 h. The peak at *m/z* 384 corresponds to the $[M_1 + H]^+$ ion of quetiapine. The peak at *m/z* 530.8 corresponds to the $[M_2 + 2H]^{2+}$ ion of Aβ(25-35). The peaks at *m/z* 400 and 416 indicate hydroxylated compounds of quetiapine and •OH in Fenton reaction solution (B) and in Aβ(25-35) solution (D).

the FEBS Journal

Demonstration of an anti-oxidative stress mechanism of quetiapine

Implications for the treatment of Alzheimer's disease

Haiyun Xu[1,2,*], Haitao Wang[3,*], Lixia Zhuang[4], Bin Yan[3], Yingxin Yu[3], Zelan Wei[3], Yanbo Zhang[3], Lillian E. Dyck[3], Steven J. Richardson[5], Jue He[3], Xiaokun Li[2], Jiming Kong[6] and Xin-Min Li[2,3,7]

FEBS Journal **275** (2008) 3718–3728 doi:10.1111/j.1742-4658.2008.06519.x

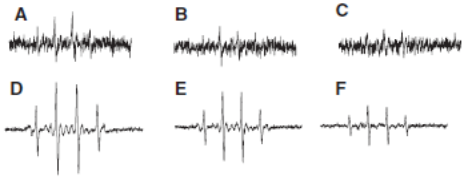


Fig. 3. Quetiapine scavenges hydroxyl radicals in Aβ(25-35) and Fenton reaction solutions. After incubation in the presence or absence of various concentrations of quetiapine at 37 °C for 24 h, Aβ(25-35) (1 mM) solutions were examined using a Bruker EMX X-band EPR spectrometer and *N*-*tert*-butyl-α-phenylnitrone as the spin trapping agent. (A) A typical four-line spectrum of free hydroxyl radicals in Aβ(25-35) solution. The intensity of the free hydroxyl radical spectra decreased in Aβ(25-35) solutions with (B) 0.5 or (C) 1.0 mM quetiapine. (D,F) The 5,5-dimethyl-1-pyrroline-*N*-oxide spectra from the Fenton reaction solutions were similarly reduced by quetiapine.

Perspectives cliniques?

Free radical scavenging activity of the antipsychotic drug olanzapine

Bastien Langrée[1], Brice Martin[2], Dany Saligaut[2], Gwenola Burgot[1,2], Josiane Cillard[2]
1- Guillaume Régnier Hospital, Department of Pharmacy, Rennes.
2- Rennes 1 University, Faculty of Pharmacy, UPRES EA 1274 "Movement, Sports, Health".

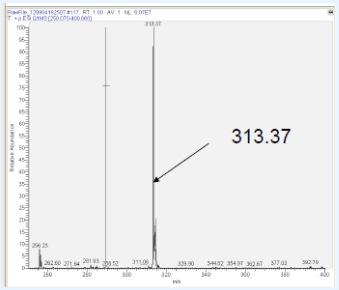


Figure 2 : Q1MS parent ion spectrum of Olanzapine in water/acetonitrile 50/50 v:v ; C_{OLZ}=0.1mM.

The theorical mass of olanzapine is 312.14086735. As expected our peak is at m/z 313.37 (mono-ionic cation). It is a relatively important peak, indeed the detector recieved 6.07^{E7} hits.
We could observe a small peak at m/z 256.23 which is probably a product of olanzapine degradation (corresponding to the transition mass commonly used in tandem mass spectrometry to identify olanzapine (MS/MS)).

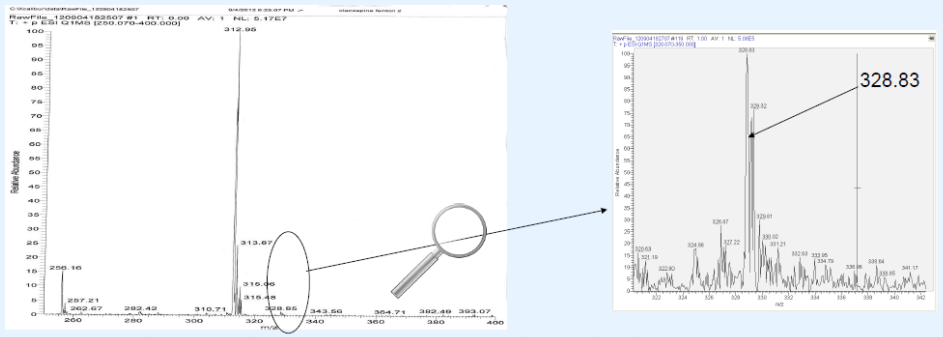
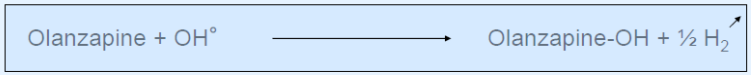
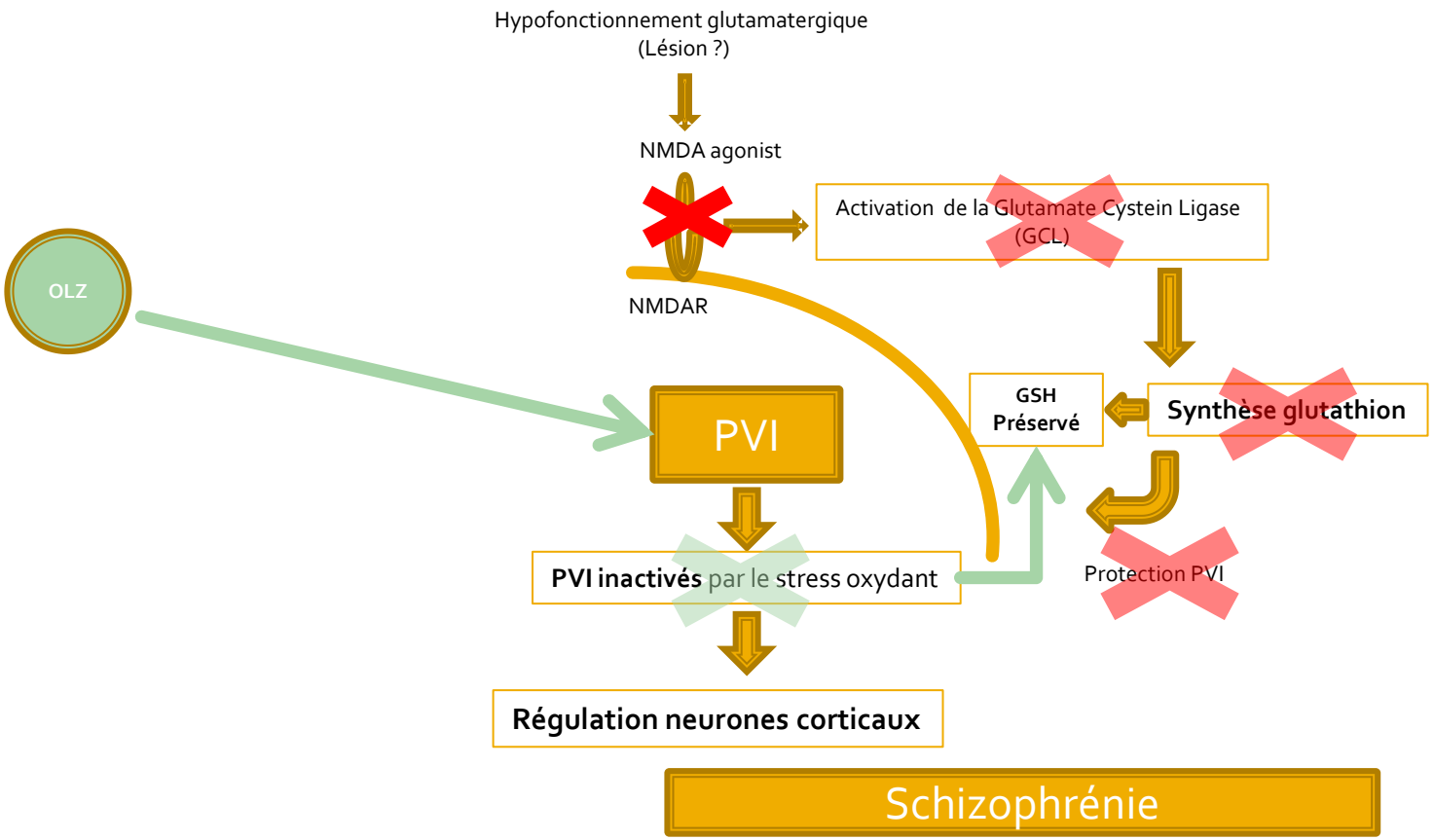


Figure 3 : Q1MS parent ion spectrum of Olanzapine in water/acetonitrile 50/50 v:v ; C_{OLZ}=0.1mM **after 2 hours of incubation in a Fenton reaction environment**.

In addition to the peak observed presiously at m/z 256 and 313, a new peak is detected at m/z 328.83, corresponding to the addition of an hydroxyl radical (m + 16) :



Perspectives cliniques?



Possible rôle de l'olanzapine

Perspectives cliniques?

Schizophrenia Research 149 (2013) 56–62

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Preventing a first episode of psychosis: Meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups

Mark van der Gaag [a,b,*], Filip Smit [a,c,d], Andreas Bechdolf [e], Paul French [f], Don H. Linszen [g], Alison R. Yung [f,h], Patrick McGorry [h], Pim Cuijpers [a]

NNT = 9

Réplication nécessaire

Table 3
Primary studies included in the meta-analysis: risk by condition, relative risk (RR), 95% confidence interval of RR, and p-value (Intention-to-Treat).

Studies included in the meta-analysis: risk by condition (12 months follow-up)

Intervention	Author	Year	Follow-up period	Experimental condition		Control condition		RR	95% CI	p-Value
				Event rate	Event %	Event rate	Event %			
Anti-psychotic medication	McGorry et al.	2002	12 months	6/31	19%	10/28	36%	.542	0.22–1.30	p = .169
	McGlashan et al.	2006	12 months	5/31	16%	11/29	38%	.425	0.16–1.08	p = .071
	McGorry et al.	2013	12 months	6/42	14%	8/28	29%	.760	0.28–2.03	p = .583
Omega-3 fatty acid	Amminger et al.	2010	12 months	2/41	5%	11/40	28%	.187	0.04–0.75	p = .019
Integrated psychological interv.	Nordentoft et al.	2006	12 months	3/42	7%	10/37	27%	.264	0.08–0.89	p = .031
	Bechdolf et al.	2012	12 months	0/63	0%	9/65	14%	.054	0.00–0.91	p = .043
Cognitive behavioral therapy	Morrison et al.	2004	12 months	2/37	2%	6/23	26%	.207	0.05–0.94	p = .041
	Addington et al.	2011	12 months	0/27	0%	3/24	13%	.128	0.01–2.40	p = .166
	McGorry et al.	2013	12 months	7/44	16%	6/28	21%	.742	0.28–1.98	p = .552
	Morrison et al.	2012	12 months	7/144	5%	10/144	7%	.700	0.27–1.79	p = .456
	Van der Gaag et al.	2012	12 months	9/98	9%	20/103	19%	.473	0.23–1.00	p = .046

ETP?

Studies included in the meta-analysis: risk by condition (medium-term follow-up: 24–48 months)

	Author	Year	Follow-up period	Experimental condition		Control condition		RR	95% CI	p-Value
				Event rate	Event %	Event rate	Event %			
	McGorry et al.	2002/2007	36–48 months	10/31	32%	12/28	43%	.753	0.39–1.47	p = .403
	Nordentoft et al.	2006	24 months	9/42	21%	14/37	38%	.566	0.28–1.15	p = .117
	Bechdolf et al.	2012	24 months	1/63	2%	10/65	15%	.103	0.01–0.78	p = .028
	Morrison et al.	2004/2007	36 months	7/37	19%	7/23	30%	.622	0.25–1.54	p = .305
	Morrison et al.	2012	24 months	10/144	7%	13/144	9%	.769	0.35–1.70	p = .516

RR = Risk ratio: 95% CI = 95% confidence interval.

Perspectives cliniques?

ORIGINAL ARTICLE

Long-Chain ω-3 Fatty Acids for Indicated Prevention of Psychotic Disorders

A Randomized, Placebo-Controlled Trial

G. Paul Amminger, MD; Miriam R. Schäfer, MD; Konstantinos Papageorgiou, MD; Claudia M. Klier, MD; Sue M. Cotton, PhD; Susan M. Harrigan, MSc; Andrew Mackinnon, PhD; Patrick D. McGorry, MD, PhD; Gregor E. Berger, MD

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- Etude randomisée vs placébo
- 81 jeunes à très haut risque
- Proportion de patients sans premier épisode

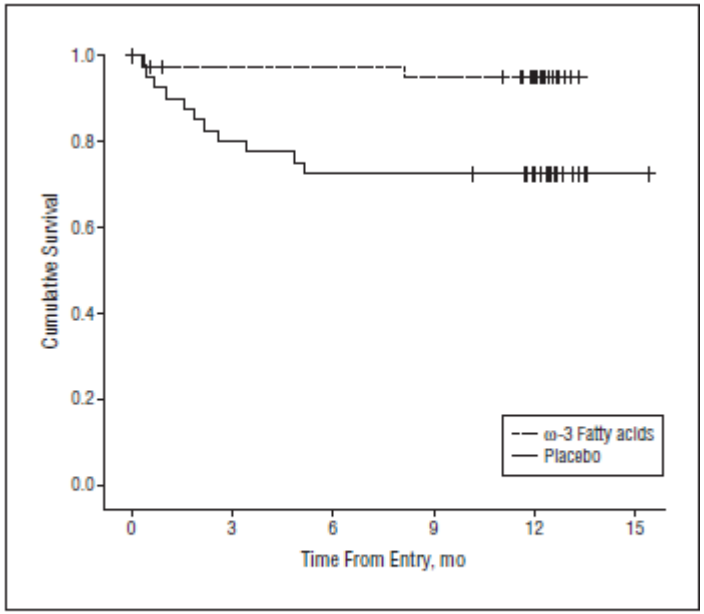


Figure 2. Kaplan-Meier estimates of the risk of transition from the at-risk state to psychotic disorder in patients assigned to ω-3 fatty acids or placebo (P=.007 by log-rank test).

Perspectives cliniques?

- Mais aussi :
  - Cytokines
  - Anticorps
  - Anti-inflammatoires
  - Etc.

Perspectives cliniques?

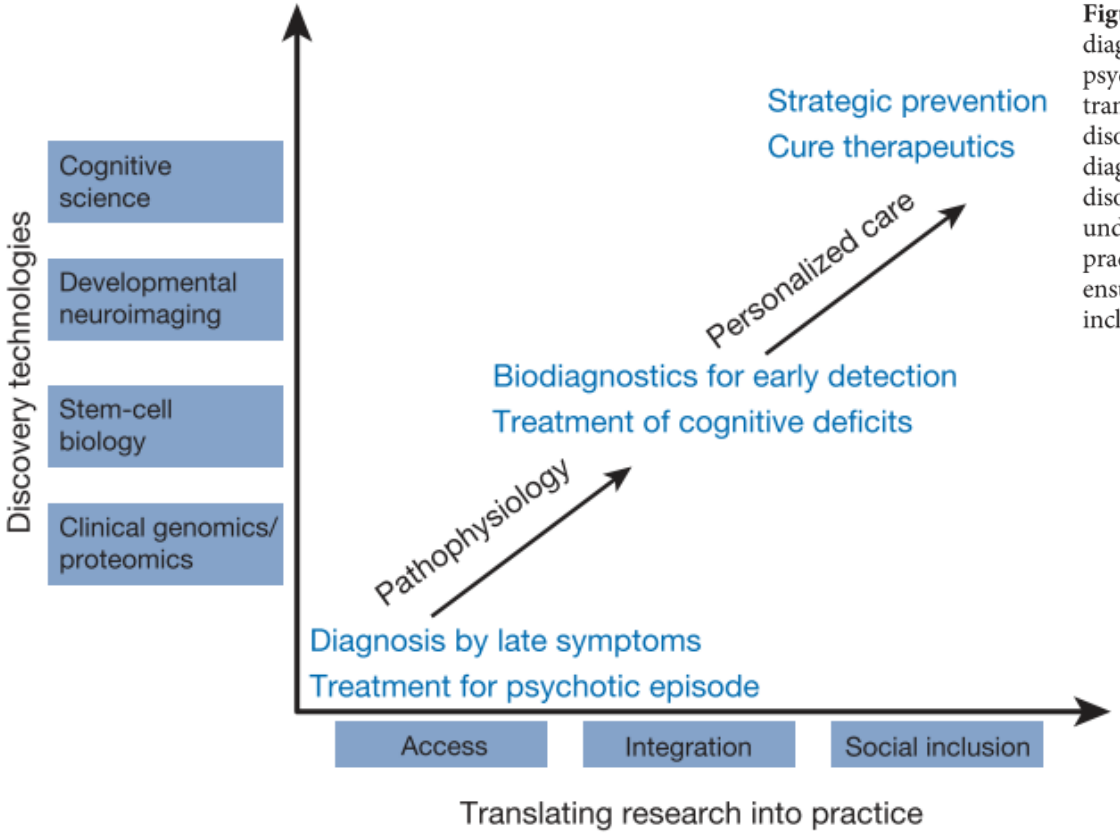


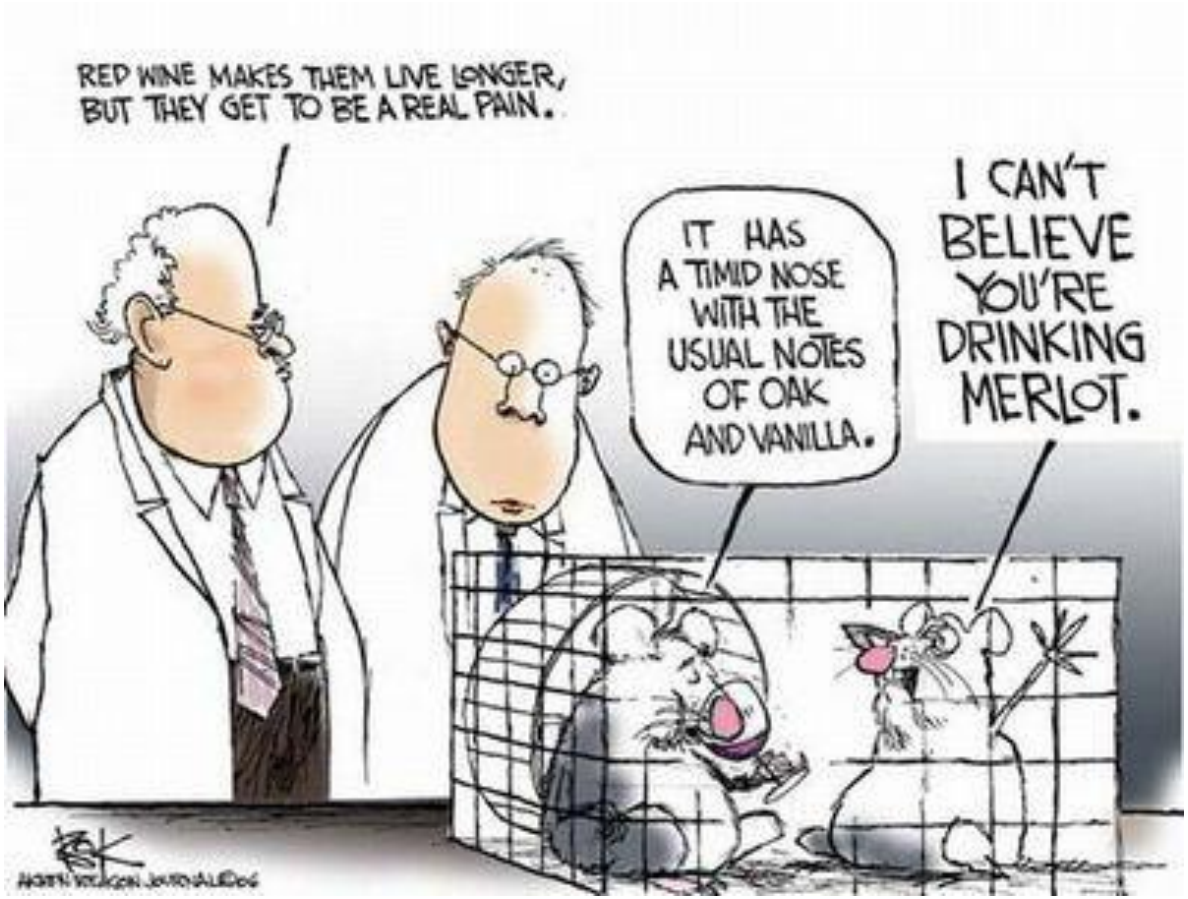
Figure 2 | A vision for schizophrenia over the next two decades. Currently diagnosis follows psychosis (stage III) and treatment focuses on reducing psychotic symptoms. The use of discovery technologies, which have already transformed the understanding and treatment of many other medical disorders, can transform our understanding of schizophrenia, yielding earlier diagnosis (stages I or II) with treatments focused on the cognitive deficits of this disorder. The ultimate goal, however, is cure and prevention based on an understanding of individual risk and the development of personalized care. In practice this means not only identifying risk and preemptive interventions but ensuring access to these interventions, integrating care and ensuring full social inclusion for people at any stage of the schizophrenia trajectory.

Insel, T.R., 2010. Rethinking schizophrenia. Nature 468, 187–193. doi:10.1038/nature09552

Conclusion

- Encore beaucoup à faire, et tant à découvrir
- Nosographie qui doit évoluer
- Promouvoir l'intervention précoce

Conclusion


RED WINE MAKES THEM LIVE LONGER, BUT THEY GET TO BE A REAL PAIN.
IT HAS A TIMID NOSE WITH THE USUAL NOTES OF OAK AND VANILLA.
I CAN'T BELIEVE YOU'RE DRINKING MERLOT.