



## Stress néonatal et barrière intestinale

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- **Déclaration d'intérêts de Mme. : THEODOROU Vassilia**

- **Activités de conseil, fonctions de gouvernance, rédaction de rapports**

*Non*

*Société(s) : .....*

- **Essais cliniques, autres travaux, communications de promotion**

*Non*

*Société(s) : .....*

- **Intérêts financiers (actions, obligations)**

*Non*

*Société(s) : .....*

- **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**

*Non*

*Société(s) : .....*

- **Réception de dons sur une association dont je suis responsable**

*Non*

*Société(s) : .....*

- **Perception de fonds d'une association dont je suis responsable et qui a reçu un don**

*Non*

*Société(s) : .....*

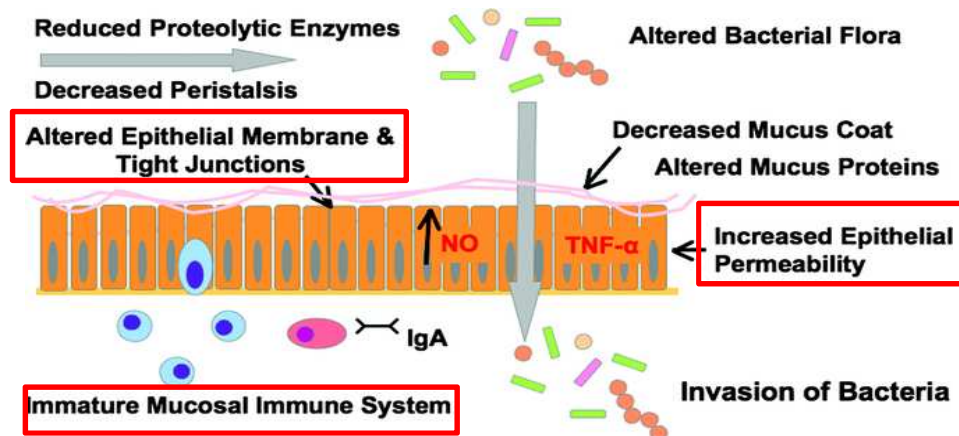
- **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**

*Non*

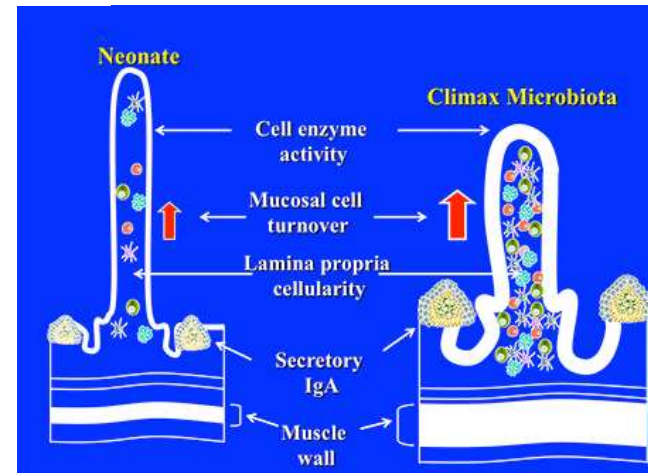
*Société(s) : .....*

*\* Effacer l'option inadéquate*

## L'intestin immature du nouveau né



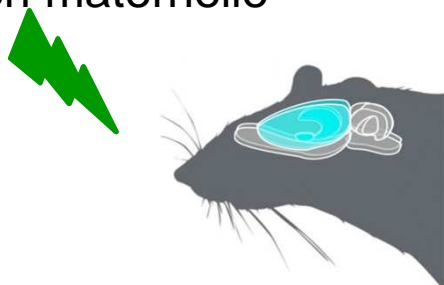
Hunter et al., 2010



Walker et al., 2011

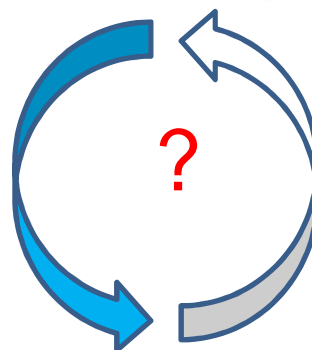
## Stress néonatal et l'axe intestin cerveau

Stress de séparation maternelle



Axe HPA « hyporéactif »

Axe HPA « réactif »

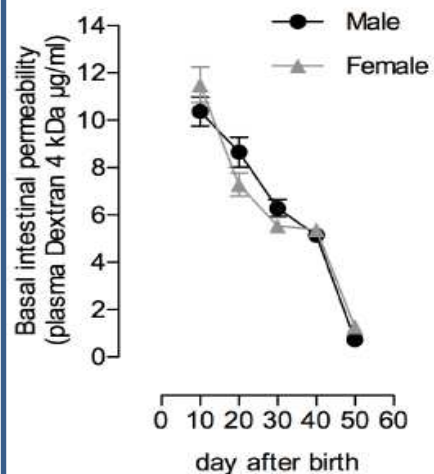


**Barrière intestinale**

# Séparation maternelle et barrière intestinale : effets à court termes

## Une séparation maternelle (SM) unique augmente la perméabilité intestinale chez le raton ...

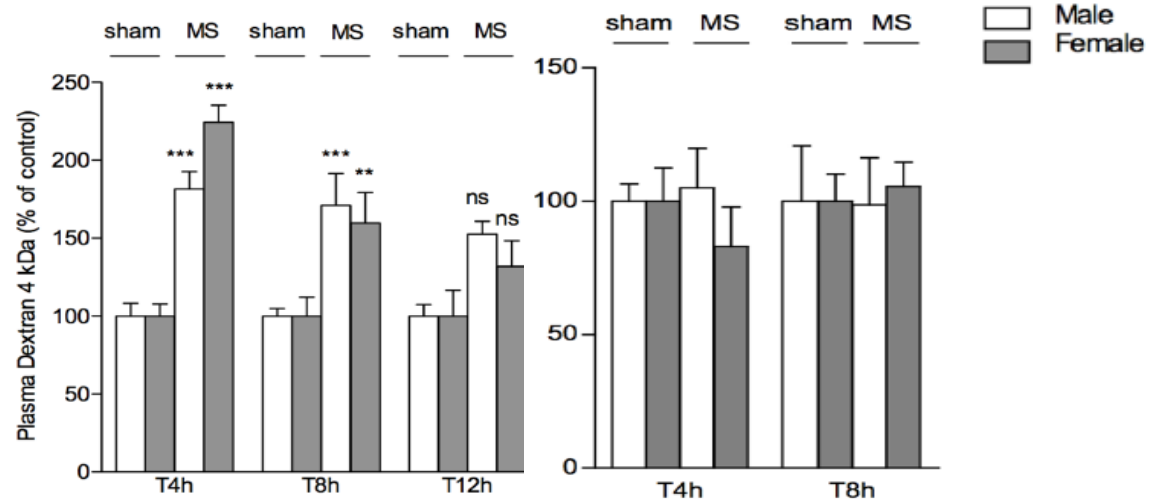
### En basal



### Après SM

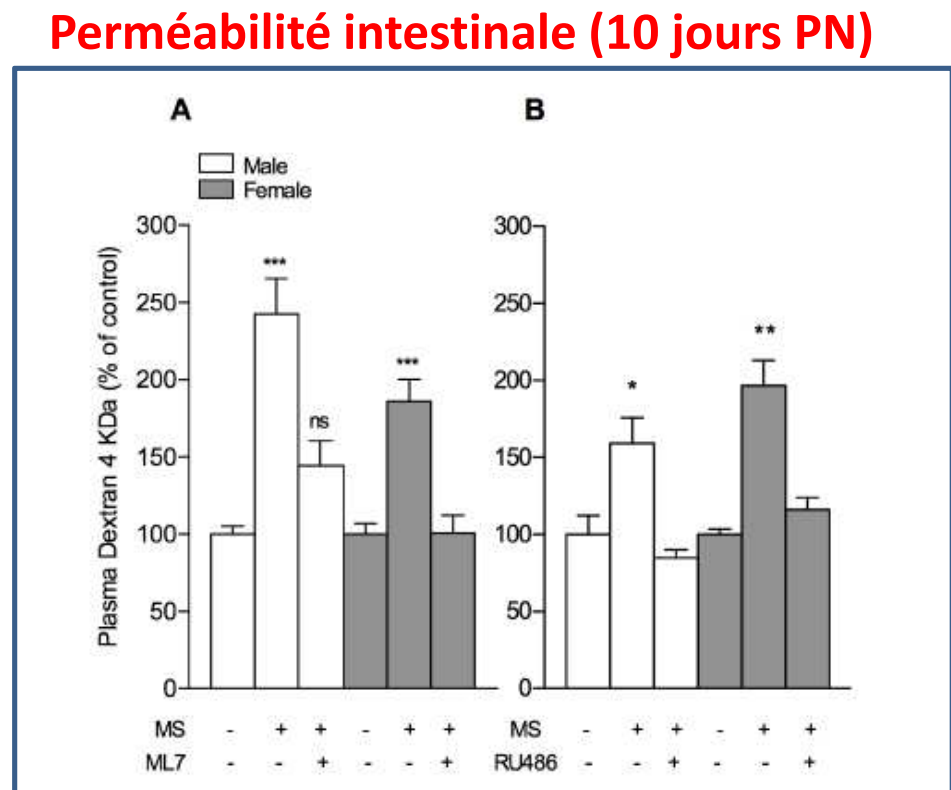
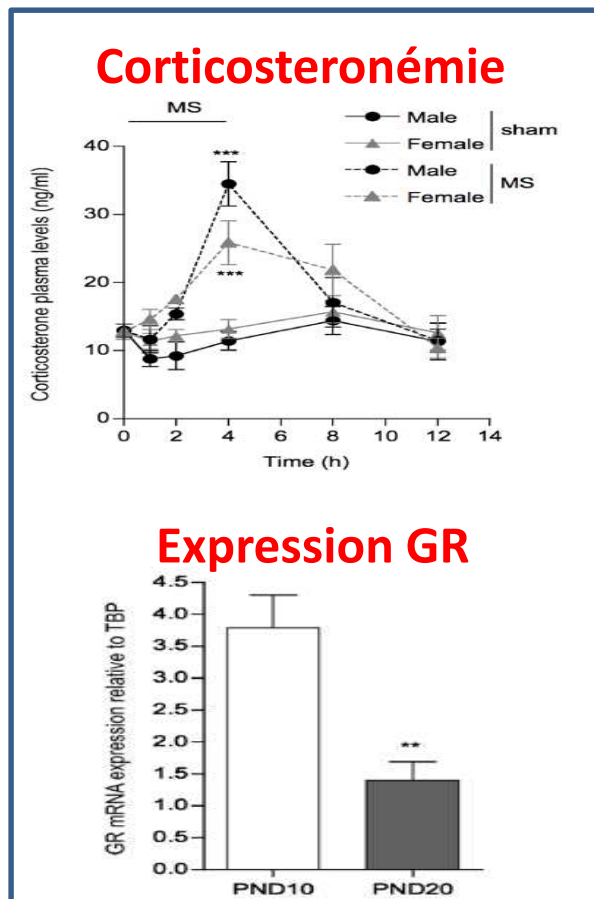
#### 10 jours PN

#### 20 jours PN



Moussaoui et al., 2014

.... via une augmentation de la contraction du cytosquelette et une activation des récepteurs aux glucocorticoïdes



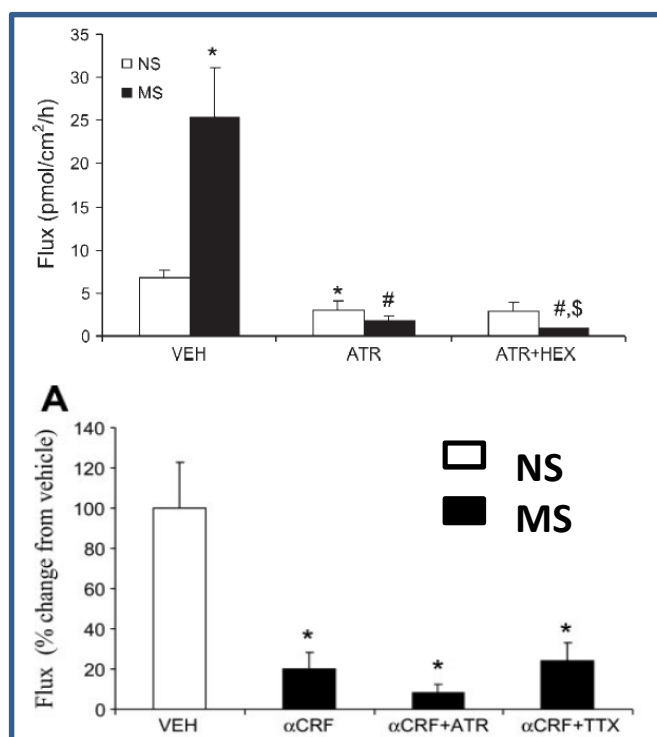
Moussaoui et al., 2014

# Neonatal maternal separation of rat pups results in abnormal cholinergic regulation of epithelial permeability

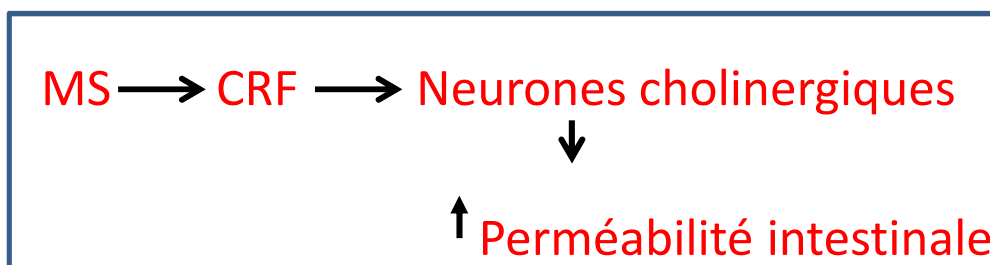
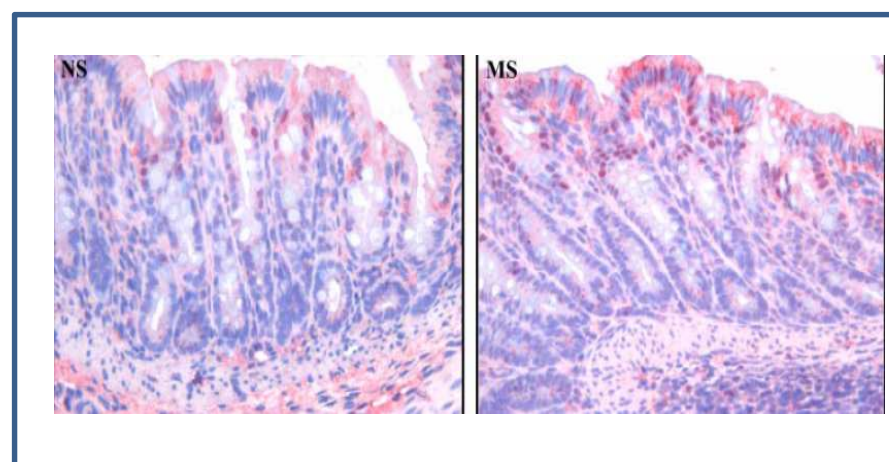
Mélanie G. Gareau, Jennifer Jury, and Mary H. Perdue

*Am J Physiol Gastrointest Liver Physiol* 293: G198–G203, 2007

## Perméabilité intestinale



## Expression de ChAT

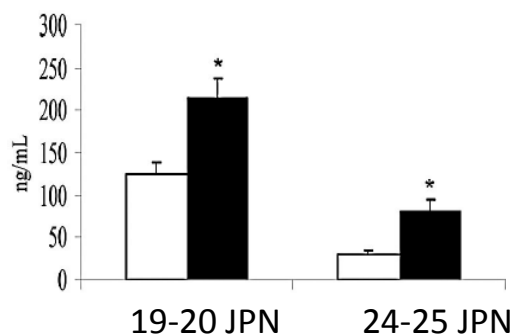




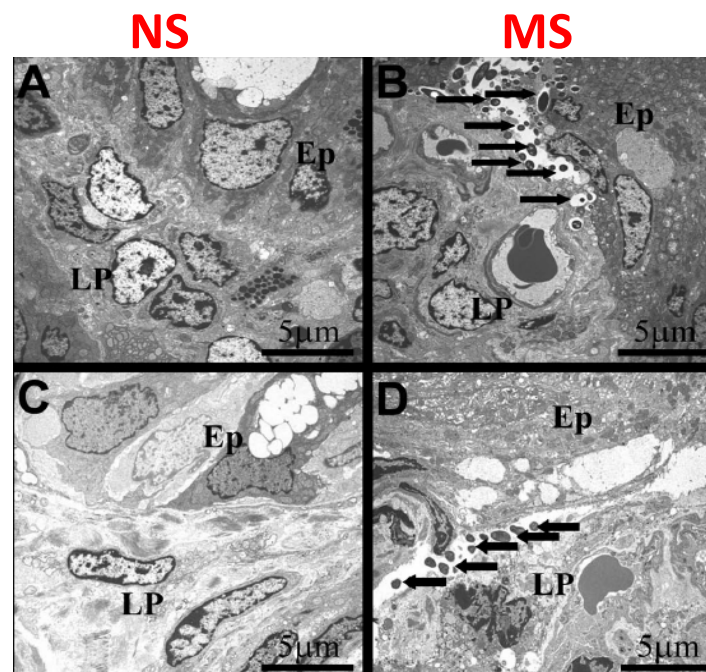
# Neonatal Maternal Separation Causes Colonic Dysfunction in Rat Pups Including Impaired Host Resistance

MÉLANIE G. GAREAU, JENNIFER JURY, PING CHANG YANG, GLENDA MACQUEEN, AND MARY H. PERDUE

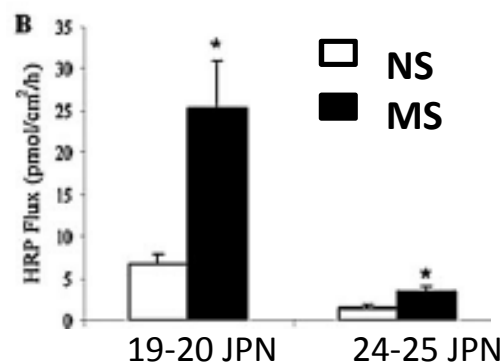
## Corticostéronémie



## Translocation bactérienne



## Perméabilité intestinale

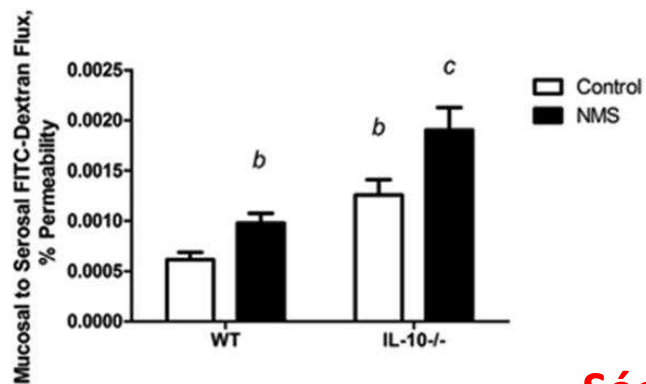


# Séparation maternelle et barrière intestinale : empreintes à long termes

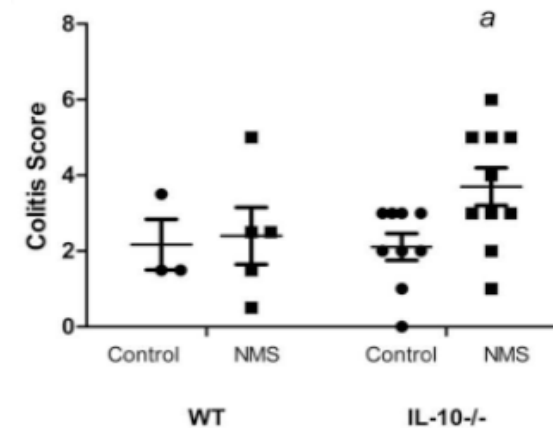
# Early Life Stress Triggers Persistent Colonic Barrier Dysfunction and Exacerbates Colitis in Adult IL-10<sup>-/-</sup> Mice

*Inflamm Bowel Dis.* 2013 ; 19(4): 712–719

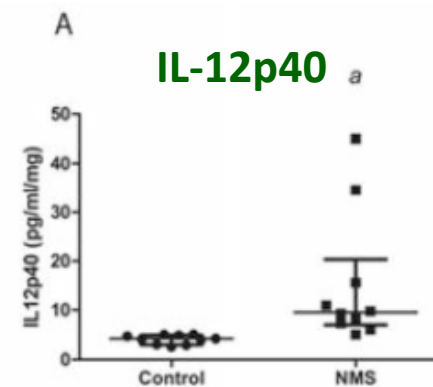
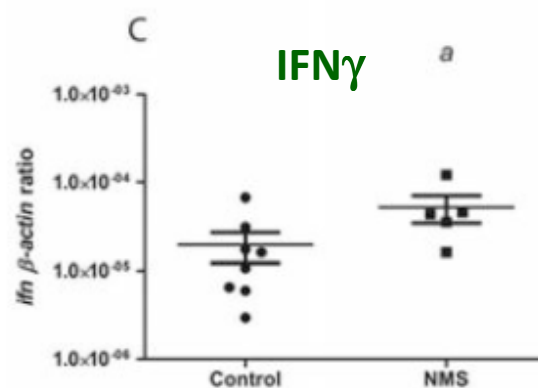
## Perméabilité intestinale



## Sévérité de la colite



## Sécrétion de cytokines



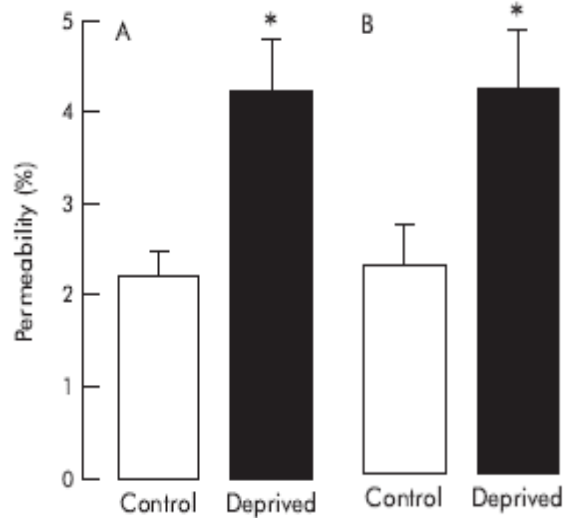
# Neonatal maternal deprivation triggers long term alterations in colonic epithelial barrier and mucosal immunity in rats

*Gut* 2004;53:501–506.

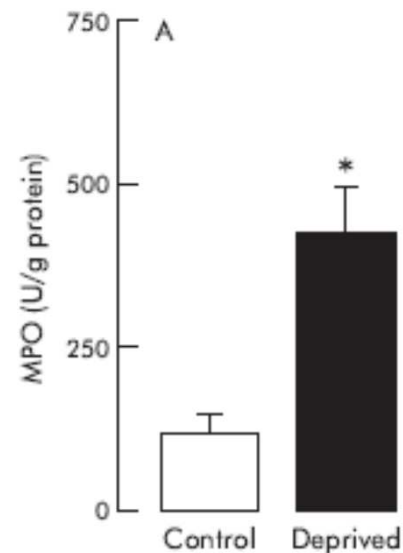
F Barreau, L Ferrier, J Fioramonti, L Bueno

Age: 12 semaines

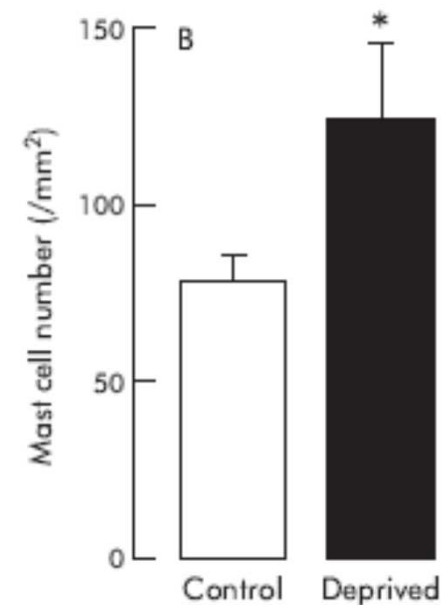
## Perméabilité intestinale



## Tonus inflammatoire



## Densité de mastocytes

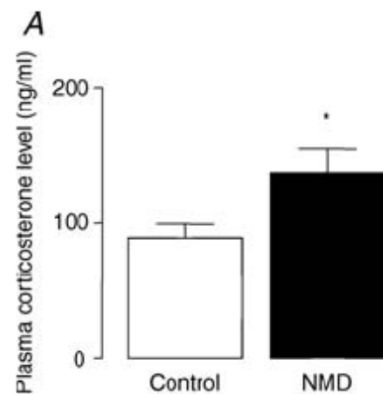


## Pathways involved in gut mucosal barrier dysfunction induced in adult rats by maternal deprivation: corticotrophin-releasing factor and nerve growth factor interplay

Frederick Barreau<sup>1</sup>, Christel Cartier<sup>1</sup>, Mathilde Leveque<sup>1</sup>, Laurent Ferrier<sup>1</sup>, Raphael Moriez<sup>1</sup>, Valerie Laroute<sup>2</sup>, Andras Rosztoczy<sup>3</sup>, Jean Fioramonti<sup>1</sup> and Lionel Bueno<sup>1</sup>

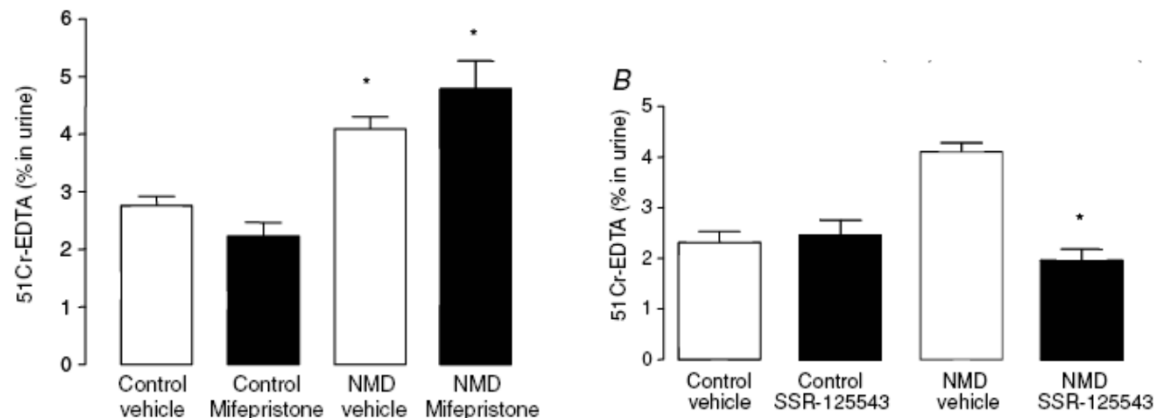
*J Physiol* 580.1 (2007)

### Corticostéronémie



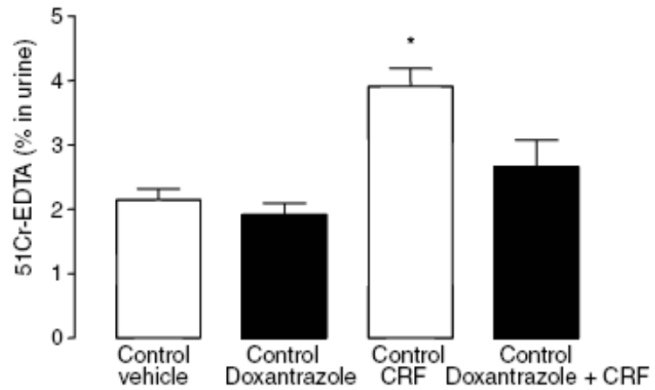
**Mifepristone: antagoniste de récepteurs aux corticoïdes**

### Perméabilité intestinale

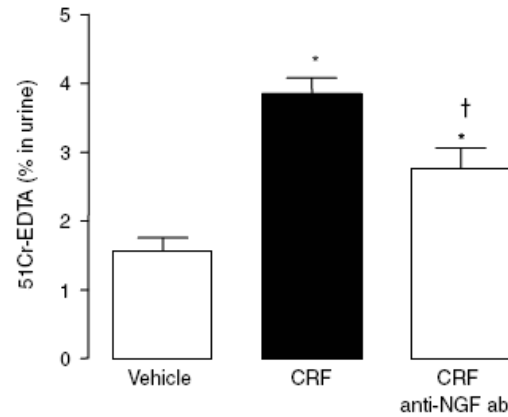


**SSR-125543: antagoniste de récepteurs CRF-R1**

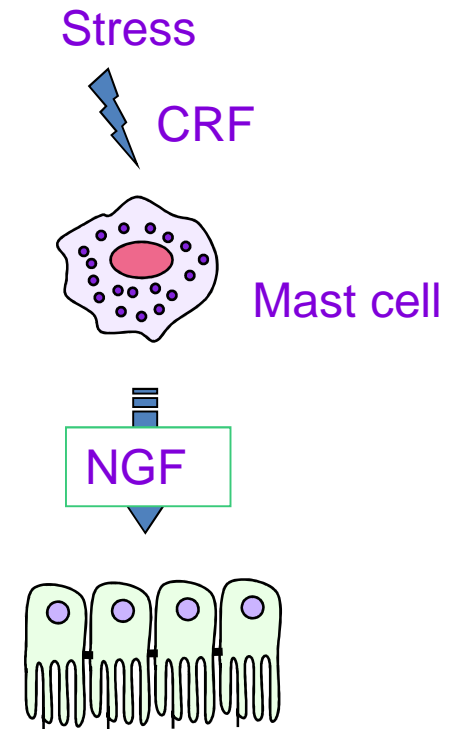
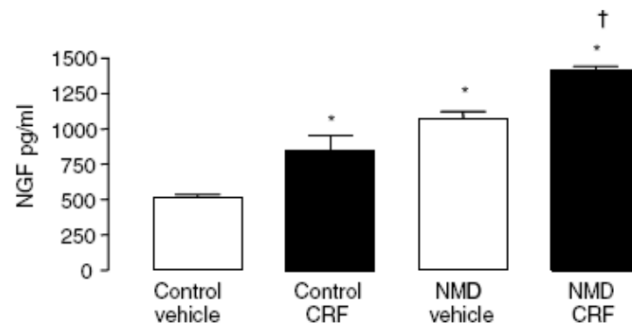
## Perméabilité intestinale



doxantrazole: stabilisateur des mastocytes



## Libération de NGF par les mastocytes



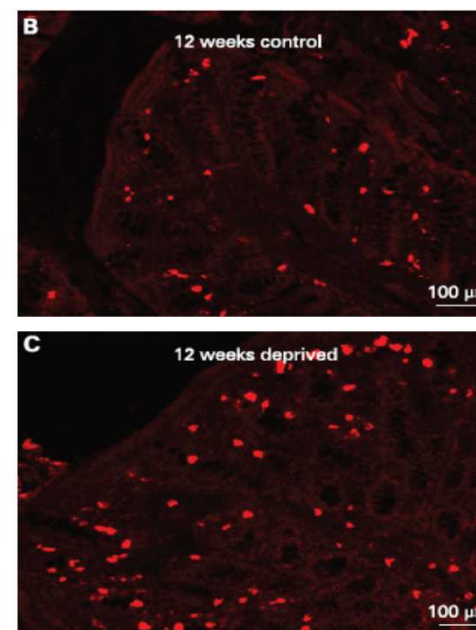
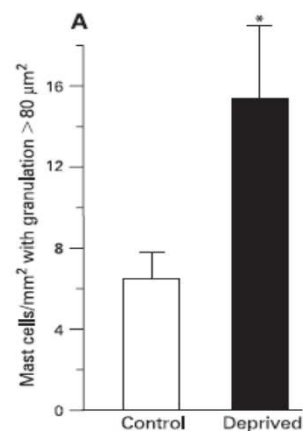
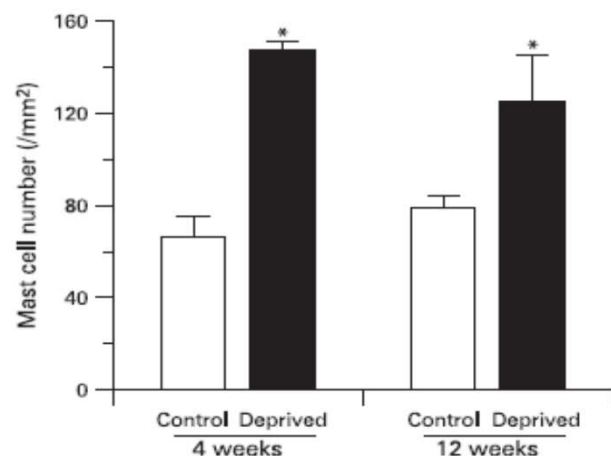


## Long-term alterations of colonic nerve mast cell interactions induced by neonatal maternal deprivation in rats

F Barreau, C Salvador-Cartier, E Houdeau, L Bueno and J Fioramonti

### La SM induit une hyperplasie et une hypertrophie mastocytaire

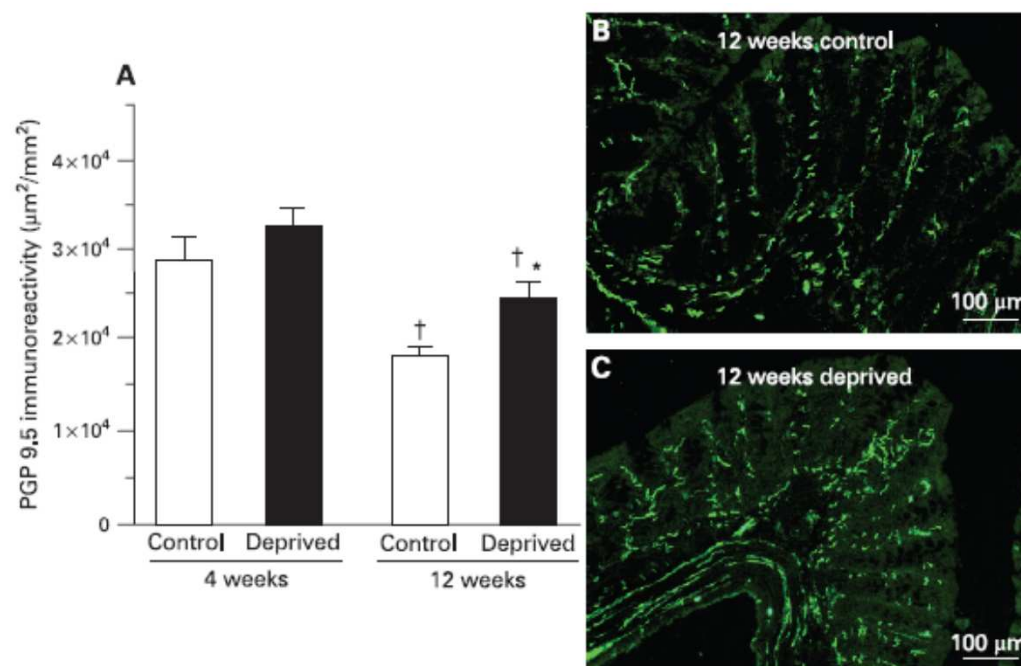
Age: 12 semaines



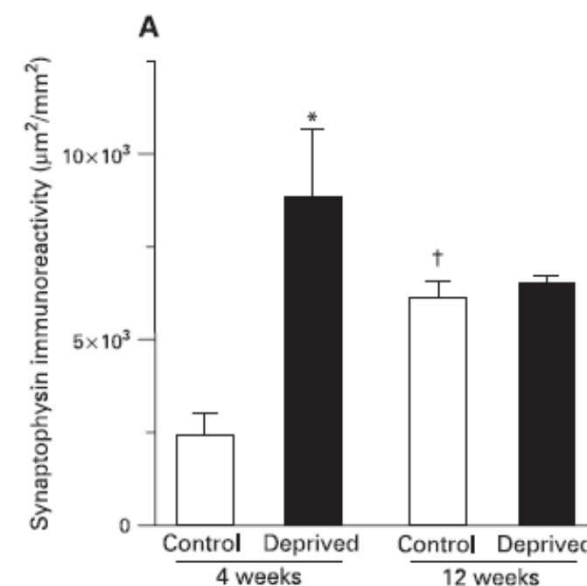
## La SM induit un remodelage de l'innervation entérique

Age: 12 semaines

### Neuroprolifération



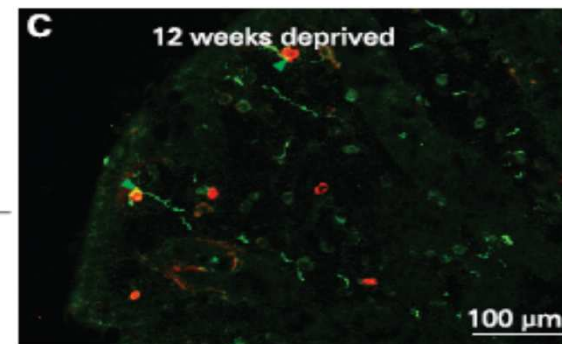
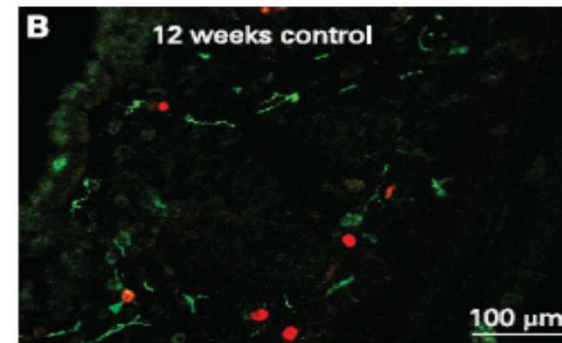
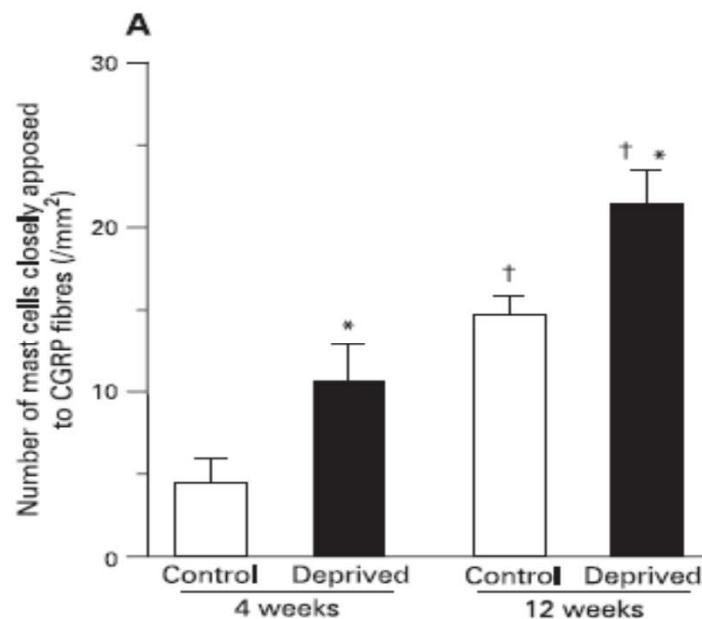
### Synaptogenèse



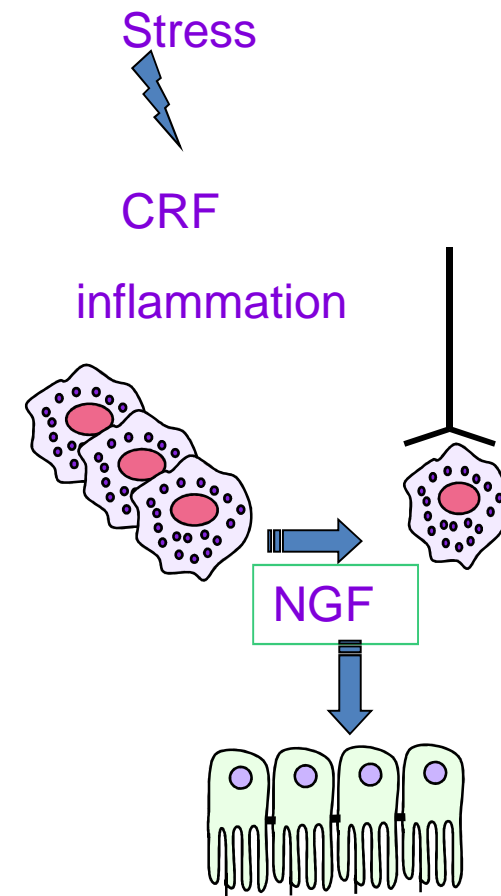
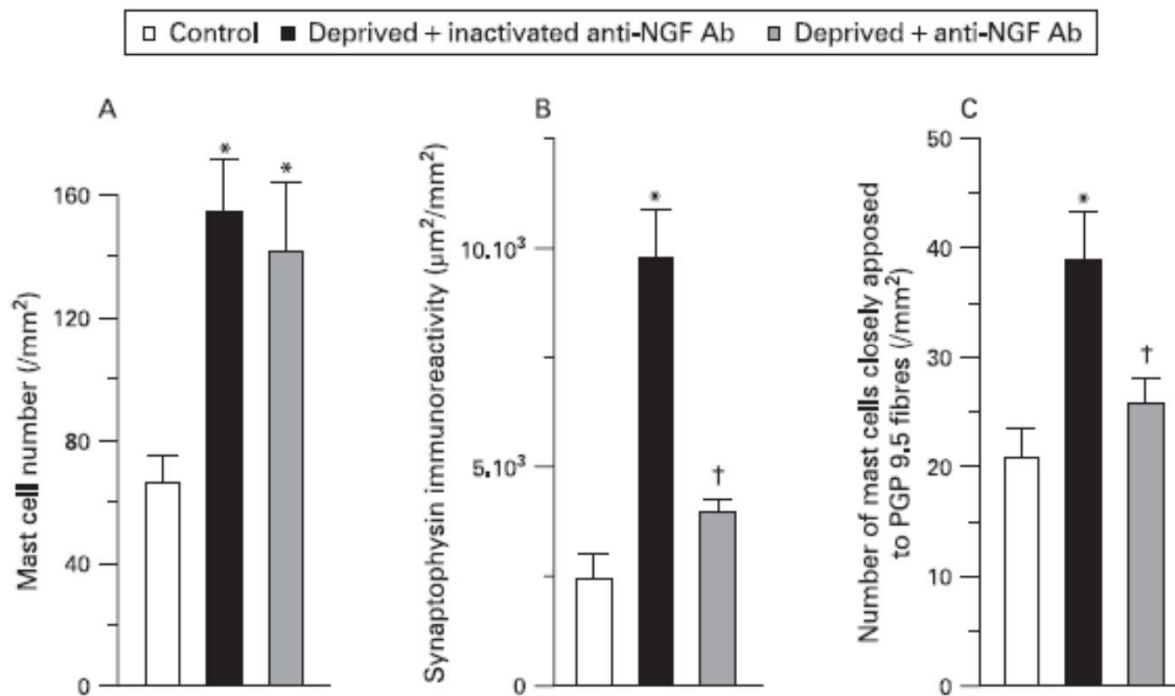


## La SM induit une juxtaposition étroite entre mastocytes et fibres nerveuses entériques

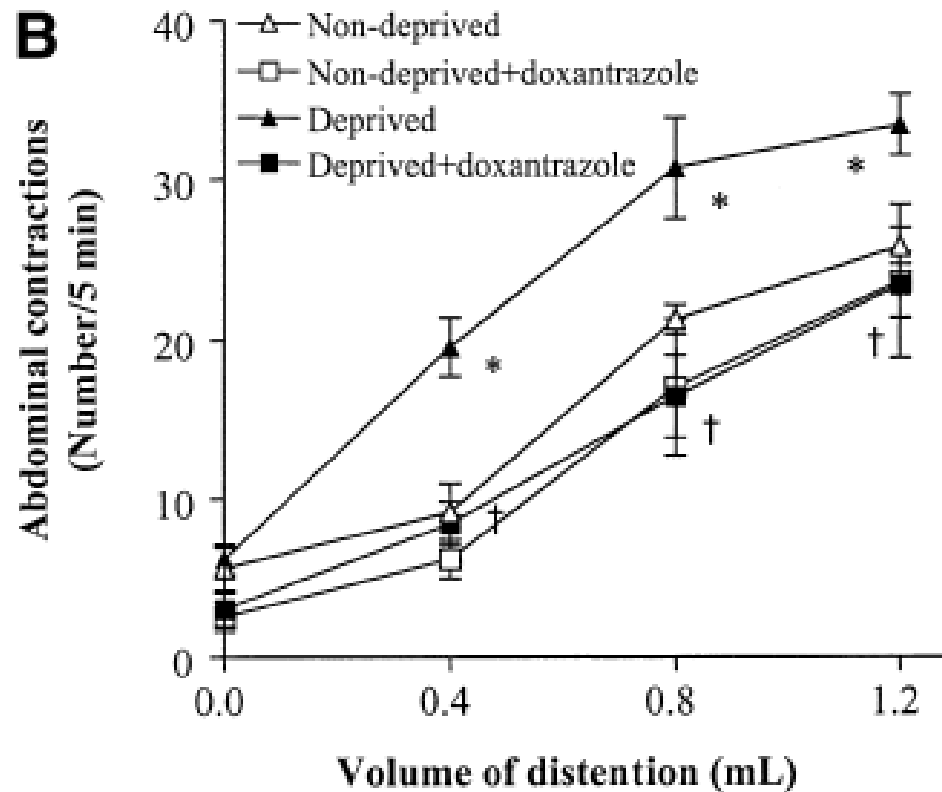
Nombre de mastocytes situées à une distance  $< 10\mu\text{m}$  des fibres PGP 9.5 immunoréactives



## Le NGF un facteur clé dans l'induction de la juxtaposition étroite entre mastocytes et fibres nerveuses entériques



## La SM induit hypersensibilité viscérale dépendante des mastocytes



Barreau et al., 2004

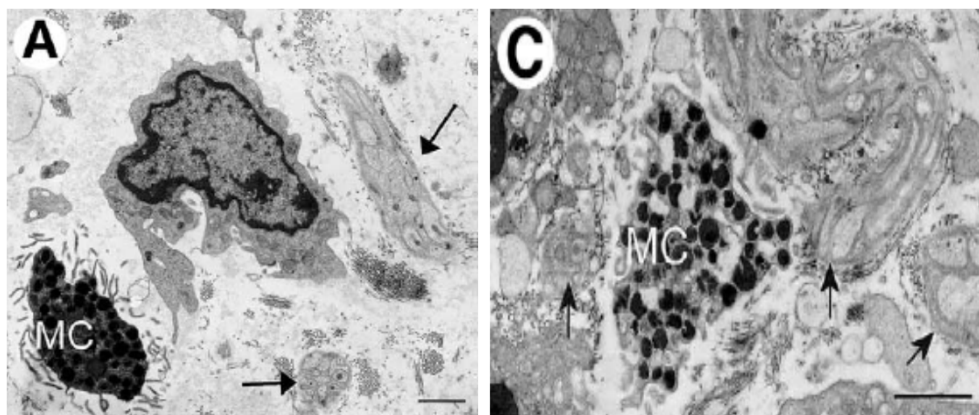
# Activated Mast Cells in Proximity to Colonic Nerves Correlate With Abdominal Pain in Irritable Bowel Syndrome

GIOVANNI BARBARA,\* VINCENZO STANGHELLINI,\* ROBERTO DE GIORGIO,\* CESARE CREMON,\* GRAEME S. COTTRELL,† DONATELLA SANTINI,§ GIANANDREA PASQUINELLI,§ ANTONIO M. MORSELLI-LABATE,\* EILEEN F. GRADY,† NIGEL W. BUNNETT,† STEPHEN M. COLLINS,¶ and ROBERTO CORINALDESI\*

GASTROENTEROLOGY 2004;126:693-702

**Contrôle**

**SII**

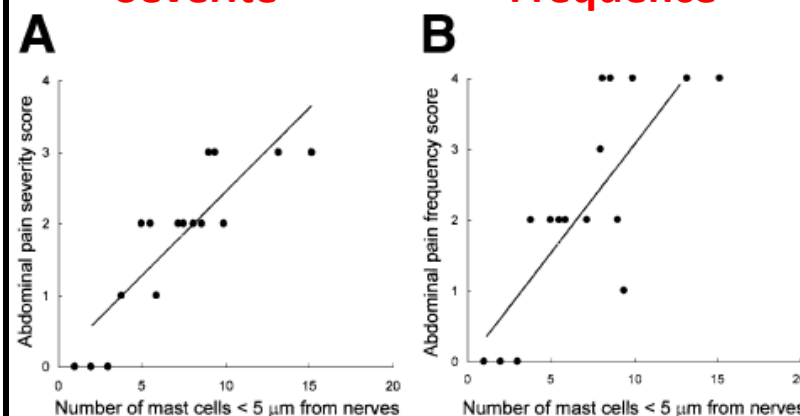


**SII: Syndrome de l'Intestin Irritable**

**Douleur viscérale**

**Sévérité**

**Fréquence**



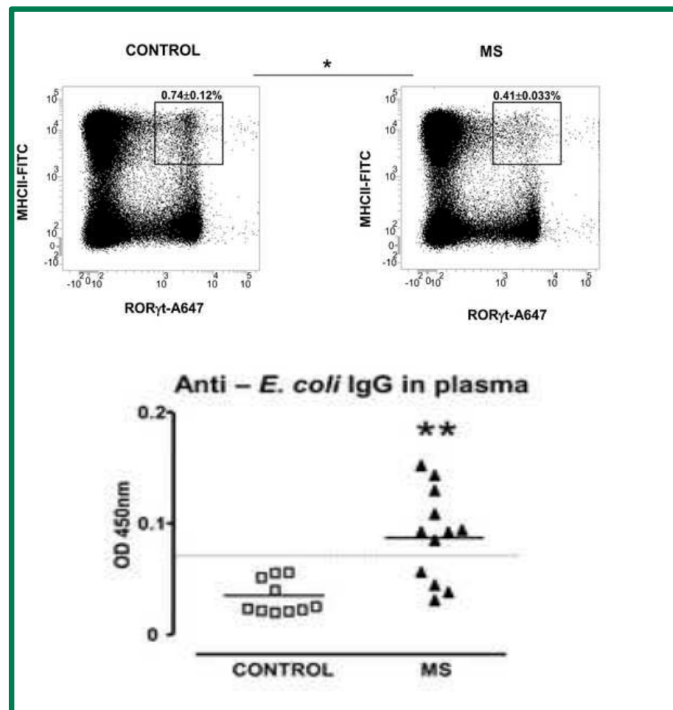
Early life stressful events weakened intestinal barrier functions leading to abnormal systemic immune response toward commensal *E. coli* population in adult mice.

A Riba, C Lencina, V Bacquié, C Harkat, M Gillet, C Cartier, M Baron, C Sommer, V Mallet, M Olier, V Théodorou, S Ménard.

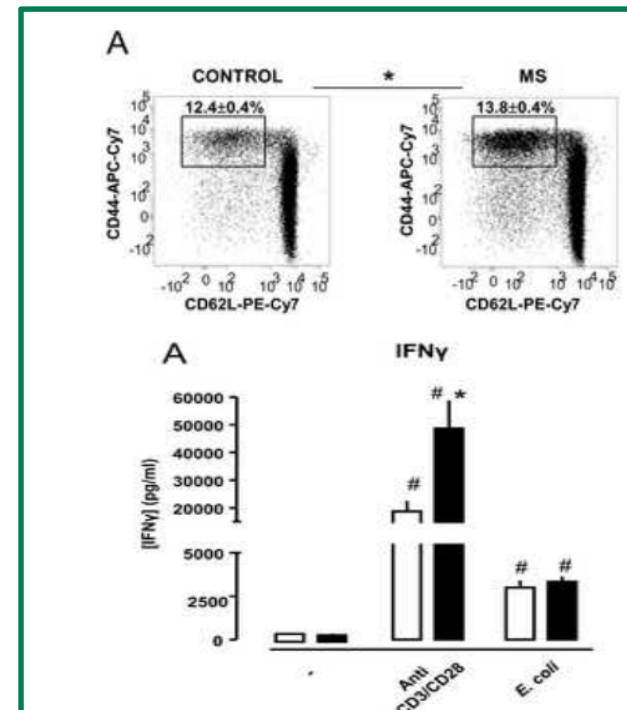
Psychoneuroendocrinology (en révision)

## Souris mâles adultes

### Réponse humorale



### Réponse cellulaire

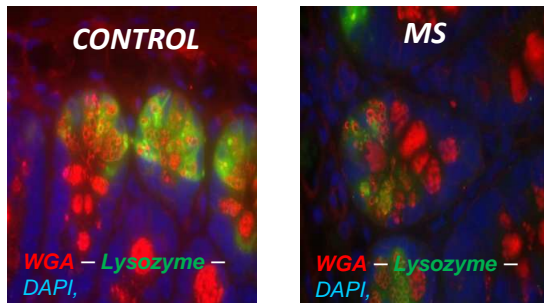


## Souris femelles adultes

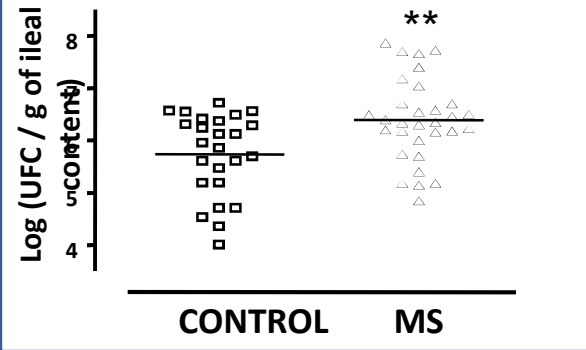
### Maternal separation

### *E. coli* gavage (adultes naïves)

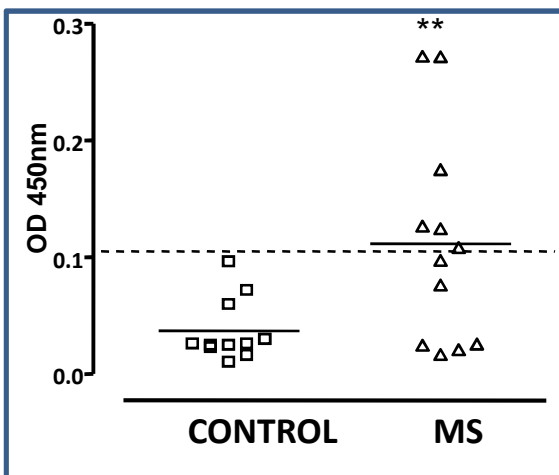
#### Lysozyme expression



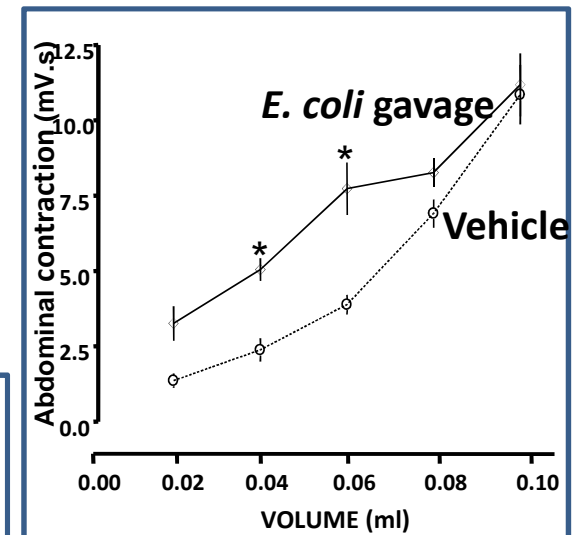
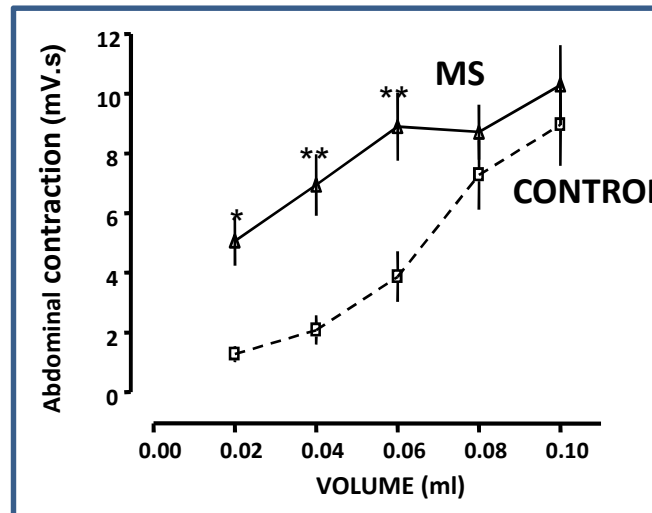
#### *E. coli* population



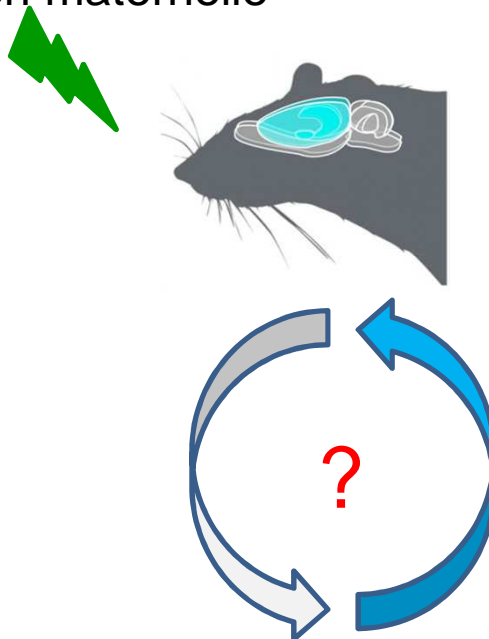
#### Anti - *E. coli* IgG in plasma



#### Viscerosensitivity



Stress de séparation maternelle



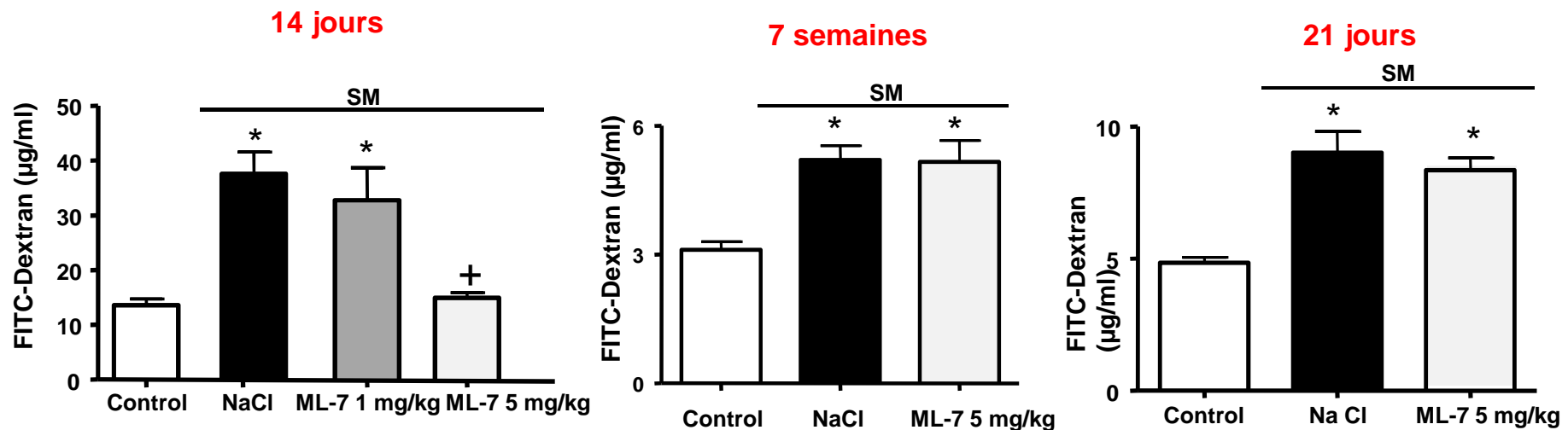
**Barrière intestinale**

# La prévention de l'hyperperméabilité intestinale induite par la SM peut-elle affecter les comportements émotionnels à l'âge adulte?



M Darnaudery  
A Mini

Traitement par ML-7 (ip) avant chaque session de SM

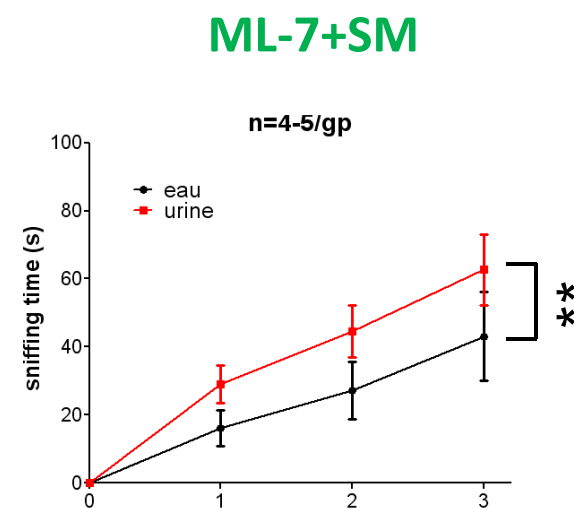
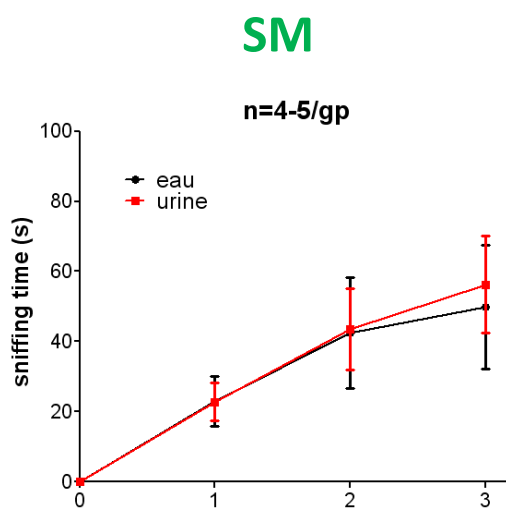
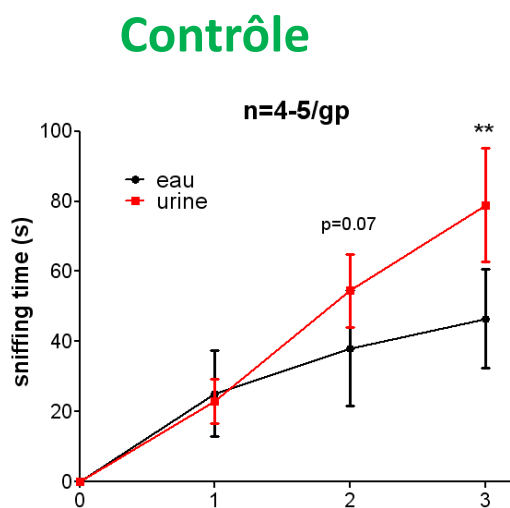




# La diminution de l'hyperperméabilité intestinale provoquée par la SM prévient les altérations de la sensibilité à la récompense sexuelle induites par ce stress précoce

## Female (in estrus) Urine Sniffing Test (reward / hedonic behavior)

Age: 3m



## Stress précoce et physiopathologie digestive

Comorbidité  
psychiatrique  
(anxiété,  
dépression...)



Axe HPA



SNA



SNE



Maladies  
intestinales  
(MICI, CD, SII...)

## Equipe Neuro-Gastroentérologie & Nutrition

