D03 – CONFERENCE PRESENTATIONS

"DEVANX" PROJECT

"Serotonin and GABA-B receptors in anxiety : from developmental risk factors to treatment"

GRANT AGREEMENT N° 201714
COLLABORATIVE PROJECT

Start date of the project: 1st February 2008
Duration: 36 months
Project Coordinator: Patricia GASPAR – INSERM
Contact : Mihaja AUGUSTE, INSERM, France, Mihaja.Auguste@inserm.fr

Document Classification

Title :	**CONFERENCE PRESENTATIONS**
Deliverable:	**DELIVERABLE NUMBER 3: D03**
Reporting Period:	**REPORTING PERIOD NUMBER 1**
Contractual Date of Delivery:	**PROJECT MONTH 12 – 31 01 2009**
Actual Date of Delivery:	**31 03 2009**

Authors	**PATRICIA GASPAR** **CO01 – INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)**
Work package	***WP1, WP2, WP5***
Dissemination	**PU [public]**
Nature	**O (Other)**
Version	***V4***
Doc ID Code	**INSERMCO01_D03_30Mar09_V4**
Keywords	**Conference, presentations, Society for Neuroscience meeting, FENS congress.**

Document History

Name	Remark	Version	Date
PATRICIA GASPAR	**Deliverable3-conference-presentations.doc**	**1**	**18/03/2009**
PATRICIA GASPAR	**Deliverable3-conference-presentationsV3.doc**	**2**	**26/03/2009**
PATRICIA GASPAR	**Deliverable3-conference-presentationsV3-3.doc**	**3**	**26/03/2009**
PATRICIA GASPAR	**Deliverable3-conference-presentationsV4.doc**	**4**	**30/03/2009**

Document Abstract

This deliverable is the presentation of our intermediate results at the FENS and Society for Neuroscience meetings.

4 Partners (INSERM, EMBL, UCC and UCO) participated to these meetings, presenting abstracts, as posters or oral presentations, presenting work in relation to the present application. There were in total 7 recorded presentations to these meetings during this first year of our contract. The abstracts are appended in the report.

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1. CONTRIBUTION OF PARTNER 1.b INSERM

Partner 1.b (INSERM U677) realized a poster presentation at FENS Congress and another poster presentation at the European Behavioural Pharmacology Society - EBPS.
These presentations are the following:

1.1 FENS Congress:

Abstract n°: 013.18
Ref.: FENS Abstr., vol.4, 013.18, 2008
Date: 13/07/2008, 09:30:00 - Hall 1
Title: ***5-HT2C receptor activation inhibits stress-induced surge of serotonin and dopamine in mesoaccumbal, but not hypothalamic areas, in mice.***
Location: Geneva, Switzerland, July 12 - 16 2008.
Authors: Mongeau R., Saurini F., Chevarin C., Hamon M. & **Lanfumey L**.
Unité de Neuropsychopharmacol., Un. Pierre et Marie Curie, Paris, France.
Abstract : Presynaptic 5-HT1A and 5-HT1B autoreceptors are known to mediate the inhibitory feedback control of serotonergic neurons through the regulation of cell firing and terminal release, respectively. Recently, electrophysiological studies in anesthetized rats suggested that 5-HT2C receptors might also participate in a negative control of 5-HT neuron firing, but, indirectly, i.e. through the activation of GABAergic interneurons. In contrast, microdialysis studies in freely moving rats did not show any inhibitory effect of 5-HT2C agonists on basal 5-HT release, although 5-HT2C-mediated inhibition of catecholamine release was often reported in the same conditions. Considering that 5-HT regulates stress responses and that, conversely, stress affects 5-HT neurotransmission, it was deemed crucial to assess the effect of a selective 5-HT2C agonist, Ro 60-0175, on the 5-HT system in basal vs. stress conditions. Adult male 129sv mice were injected with 3 mg/kg i.p. of Ro 60-0175 or saline 30 min before being placed in a restraining device for 45 min prior to sacrifice; other mice were injected but not stressed. The nucleus accumbens, the hypothalamus and the ventral tegmental area/substantia nigra (VTA/SN) were dissected out and tissue levels of 5-HT, 5-HIAA, DA, DOPAC and HVA were measured using HPLC coupled with electrochemical detection. Restraint stress increased the turnover rate of 5-HT and DA (as assessed by 5-HIAA/5-HT, DOPAC/DA and HVA/DA ratios, respectively) in all the structures tested. The administration of Ro 60-0175 significantly attenuated stress induced 5-HT and DA activation in the nucleus accumbens and the VTA/SN, but not in the hypothalamus. However, Ro 60-0175 had no effect on either monoamine in basal conditions. Considering that 5-HT2C agonists are often anxiogenic, the stress-induced increase in 5-HT (and DA) turnover in the mesoaccumbal regions might be an adaptation response which is limited by – indirect – inhibitory feedback from 5-HT2C receptors.

2. CONTRIBUTION OF PARTNER 2 EMBL

Partner 2 presented two posters at Society for Neuroscience Meeting 2008.
Here are the abstracts of these two posters:

2.1 Society for Neuroscience Meeting, Poster 1:

Program#/Poster#: 845.22/Z17
Title: ***HDAC4 moderates the maternal programming of anxiety-related behavior in mice***
Location: Washington Convention Center: Hall A-C
Presentation time: Wednesday, Nov 19, 2008, 2:00 PM - 3:00 PM
Authors: T. FERREIRA, V. CAROLA, R. PAOLICELLI, ***C. T. GROSS**; Mouse Biol. Unit, EMBL, Monterotondo (RM), Italy
Abstract: Early adverse experiences are known to increase the risk for a range of negative health outcomes. Recent data demonstrate that exposure to altered maternal care early in life can persistently alter chromatin structure associated with the transcriptional state of specific genes. Here we investigated whether heterozygous null mutations in the chromatin modulator, histone deacetylase 4 (HDAC4), could alter the maternal programming of anxiety-related behavior. We have previously established a breeding paradigm that allows for the behavioral testing of genetically homogeneous cohorts of mice that have been exposed to either high or low levels of maternal licking and grooming. Mice experiencing low licking and grooming show increased innate anxiety-related behavior as assessed in the open field and elevated plus maze tests. Mice carrying the HDAC4 mutation did not show alterations in anxiety-related behavior in the presence of high maternal care. However, HDAC4 mutant mice failed to show increased anxiety-related behavior following exposure to low maternal care. These findings suggest that the capacity of an animal to promote histone deacetylation is critical to determining the long-term effects of early environmental exposure and confirms the important role of epigenetic regulation in the developmental programming of behavior.

2.2 Society for Neuroscience Meeting, Poster 2:

Program#/Poster#: 845.2/Y31
Title: ***Role of hippocampal dentate gyrus circuits in innate anxiety-related behavior tested using a novel emergence test***
Location: Washington Convention Center: Hall A-C
Presentation Time: Wednesday, Nov 19, 2008, 2:00 PM - 3:00 PM
Authors: *A. JAIN1, T. TSETSENIS1, E. FONIO2, A. DVORKIN2, I. GOLANI2, **C. GROSS1**; 1Mouse Biol. Unit, European Mol. Biol. Lab., Monterotondo(Rome), Italy; 2Dept. of Zoology, Tel-Aviv Univ., Tel-Aviv, Israel
Abstract: Anxiety is a fundamental emotion shared by all animals that plays an essential role in modulating defensive behaviors. In the mouse, innate anxiety-related behavior is routinely measured by assessing avoidance and risk assessment behavior in an unfamiliar environment. Here we used a large circular open field attached to a home cage as a test to measure approach/avoidance exploratory behavior in mice. The inclusion of a home cage allows the animals to choose when to explore the unfamiliar environment and results in a stereotyped and gradual exploration of the open arena over a period of one hour. Pharmacological validation with anxiolytic drugs was used to define anxiety-related exploratory measures in the test. Further experiments examined the effects of prior handling and familiarity on exploratory behavior. Unbiased and detailed analysis of locomotor trajectories and measures during exploration were analyzed using SEE (Software for the Exploration of Exploration) workshop computational tools. Finally, we have applied pharmacogenetic neural inhibition tools to examine the role of hippocampal dentate gyrus granule cells in the control of exploratory behavior.

3. CONTRIBUTION OF PARTNER 4 UCC

Partner 2, University College Cork, attended two meetings: Society for Neuroscience Meeting and FENS Congress. These presentations were not directly funded by DEVANX but are DEVANX-related.

3.1 Society for Neuroscience meeting:

Gibney SM, Gosselin RD, O'Malley D, Dinan TG & **Cryan JF** Altered cortical cellular activation in an animal model of early-life stress: Effects of psychological and colorectal distension -induced stressors in adulthood Program No. 269.1. 2008 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2008. Online

Gosselin RD, Dwyer, N., P. Fitzgerald, Dinan TG & **Cryan JF** Altered spinal expression of the astrocytic glutamate transporter EAAT1 in the rat maternal separation model of visceral hypersensitivity Program No. 269.3. 2008. Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2008. Online

McKernan DP, O'Connor R, Browne C, Dinan TG & **Cryan JF** Lipopolysaccharide induces hippocampal cell death in the mouse: Effects of strain. Program No. 452.19. 2008. Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2008. Online

3.2 FENS Congress:

Organiser and Chair Symposium "New insights into Cortico-Amygdala interactions: implications for disorders of emotion" FENS Meeting Geneva, Switzerland, July 2008.

4. CONTRIBUTION OF PARTNER 5 UPO

Partner 5, Universidad Pablo de Olavide, had two presentations at the FENS Congress and none at the Society for Neuroscience Meeting for 2008.
The FENS Meeting presentation are the following:

4.1 FENS Congress, Oral presentation:

Title: ***TrkB and the PLCgamma-site activated signalling pathway are central to both long-term potentiation and learning. Symposium*** **on** ***Recent advances in neurotrophin signalling at central synapses****.*
Location: Geneva, Switzerland: *6th FENS, Forum of European Neuroscience*.
Authors: Minichiello, L.M., **Gruart, A.**, Sciarretta, C.S., Valenzuela-Harrington, M. and **Delgado-García, J.M.** (2008).
Abstract: Oral presentation in the Symposium on Recent advances in neurotrophin signaling at central synapses. In collaboration with Liliana Minichiello (from Rome), we studied if the molecular pathways required for learning are also those generating long term potentiation (LTP) when measured directly on the relevant circuit of a learning animal is clearl important. With the combination of in vivo methods we showed that signaling through the TrkB receptors is important for associative learning and parallel LTP.

4.2 FENS Congress, Poster presentation:

Title: ***Altered prepulse inhibition and increased anxiety in mGluR1 knockout mice correlate with a deficit of parvalbumin-immunoreactive interneurons in prefrontal cortex and hippocampus.***
Location: Geneva, Switzerland: 6th FENS, Forum of European Neuroscience.
Authors: Fairén, A., **Gruart, A., Delgado-García, J.M.**, Cortés, M. and Gil-Sanz, C. (2008).
Abstract: Poster presentation with the prenatal stages when mice can present possible disturbances in the generation and/or migration of cortical interneurons in wild type and mGluR1 KO mice. We observed a diminution in the interneuron production in basis of the GABAergic depletion in KO mice, which correlates with deficiencies at the behavioural and physiological levels.