Neuropsychopharmacologie des addictions : vulnérabilité et variabilité expérimentale et clinique

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

Evaluation report

Research unit

Neuropsychopharmacologie des Addictions :

Vulnérabilité et variabilité expérimentale et clinique

University Paris 5

March 2009

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Neuropsychopharmacologie des Addictions : Vulnérabilité et variabilité expérimentale et clinique

University Paris 5

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2009

Evaluation report

The research unit :

Name of the research unit : Neuropsychopharmacologie des Addictions: Vulnérabilité et variabilité expérimentale et clinique

Requested label : UMR_S INSERM, UMR CNRS

N° in case of renewal : INSERM U 705 UMR CNRS 7157

Head of the research unit : M. Jean-Michel SCHERRMANN

University or school:

University Paris 5

Other institutions and research organization:

CNRS

INSERM

CEA

University Paris 7

Date of the visit :

3 February 2009

Members of the visiting committee

Chairman of the committee :

M. Jean-Pol TASSIN, Collège de France, Paris

Other committee members :

Ms. Brigitte KIEFFER, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Strasbourg

M. Bruno AOUIZERATE, Centre Hospitalier Charles Perrens, Bordeaux

M. David BEGLEY, Center for Neuroscience Research, King's College London, UK

M. Rafael MALDONADO, Université de Pompeu Fapra, Barcelone, Espagne

CNU, CoNRS, CSS INSERM, INRA, INRIA, IRD representatives :

M. Alain GARDIER, CoNRS representative

Ms. Jane-Lise SAMUEL, INSERM CSS representative

Observers

AERES scientific representative:

Ms. Jocelyne CABOCHE

University or school representative:

Ms. Martine AIACH, Université Paris 5

M. Arnaud DUCRUIX, Université Paris 5

M. Frederic DARDEL, Université Paris 5

Research organization representative (s) :

Ms. Catherine LABBE-JULLIE, Chargée de mission INSERM

Ms. Nathalie LERESCHE, DSA CNRS

Evaluation report

1 • Short presentation of the research unit

The research agenda of the unit is focused on Addiction, which is recognized as being a major public healthy problem. Three teams which range from preclinical animal models and neurobiological aspects (team # 1), pharmacokinetic and blood-brain barrier analysis (team # 2) to clinical aspects with epidemiological and pharmacogenetics studies in severely addicted patients (team # 3) constitute this unit. In addition, two external teams will be included, one which has been working on biology of prion diseases (EA 3621) and whose members will be included in teams # 1, 2 and 3 and an other team in the SHFJ-CEA at Orsay highly experienced in Pharmacological imaging whose members will be included in team # 2.

Up to now laboratories were located in two sites (Faculté de Pharmacie, Avenue de l'Observatoire, Paris, teams # 1 and 2, and Hôpital Lariboisière- F. Widal, Paris, team # 3). One of the two new teams - Pharmacological imaging- is located at Orsay which will make a third site. However, in addition to regular meetings within each team, bi-monthly unit meetings assure the coherence between the members of the three teams.

- Numbers of lab members : 51 including
  - 18 researchers with teaching duties
  - 7 full time researchers
  - 3 postdoctoral fellows
  - 10 engineers, technicians and administrative assistants : 2
  - 10 PhD students : all with a fellowship
- Number of HDR : 12, including 8 who are PhD student supervisors
- Number of students who have obtained their PhD during the past 4 years : 16
- Average length of a PhD during the past 4 years : 3,4 years.
- Number of "publishing" lab members ; 28 (5 in team 1, 11 in team 2, 12 in team 3)

As a general comment, this unit had only three permanent full time scientists belonging to CNRS and none from Inserm up to date. However, because of the arrival of the two new teams, 4 permanent scientists from the CEA will join. Altogether this will finally make only 25 % of permanent scientists not in charge of teaching.

2 • Preparation and execution of the visit

The visiting committee obtained written report of the past activity (2005-2008) of the unit and the description of the project to be funded (2010-2013) well ahead of the visit. The members had become thoroughly acquainted with the material. The task was further clarified at the start of the visit by the AERES representative. The head of the unit along with the three group leaders successively gave reviews of their past results and future plans, which was helped by the booklet containing the slides. The committee met with the University presidents and representative of the IFR, who helped to understand the significance of the unit and the basis of the support the unit has and will then receive. Finally, the visiting committee was divided into three groups to discuss with researchers, students and technicians. As mentioned above, the unit is located in three separate sites. The visit occurred at the Faculty of Pharmacy, Avenue de l'Observatoire, in Paris. Unfortunately, probably because of lack of time, the committee had not the opportunity to visit the laboratories. The preparation and execution of the visit was, however, carried out professionally maintaining a relaxed but critical atmosphere.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The scientific project is designed to identify the neurobiological, pharmacokinetic and pharmacogenetic factors which influence the addiction pathways and are thus responsible for vulnerability to drugs of abuse. This is a critical public health problem that requires collaboration between basic and clinical research. The unit comprises three teams "Neurochemistry and Neurobiology of Addictions" (team # 1), "Neuropharmacokinetics and Neurotoxicity of Drugs and Metabolites. Protective role of ABC Transporters in the Blood-Brain Barrier (BBB)" (team # 2) and "Variability of response to Psychoactive Substances: Intra- and interindividual factors" (team # 3). The members appeared full of positive energy, and there seemed to prevail an open scientific discussion between the team leaders, postdocs, preclinical and clinical students. The group has established a solid publication record on addiction origin and effects, but a breakthrough into the highest profile journal is awaited. As mentioned above most of the unit consists of scientists who have also quite large teaching loads. Some of them need to establish themselves internationally more strongly, for which they certainly have the potential. The members and PhD students of the unit participate in French neuroscience and addiction meetings, and the leaders are also active at both national and international scientific committee and international conferences (for example, SC MILDT and organizer, team # 1). Additionally, they are engaged in intensive research collaborations with the university of Tohoku, Japan (courses and exchanges of students, team # 2) or EMEA (team # 3). There is still more room for international scientific collaborations. Relationships with French industry (pharmaceutical groups) are well developed, partly because this unit is firstly located at the Faculty of Pharmacy and secondly an important number of scientists, including the unit leader, are pharmacists or medical practitioners.

4 • Specific appreciation team by team and/or project by project

The plans of the unit have been formulated so that all the functions would support one main goal, i.e. the factors responsible for vulnerability and variability, focusing on the neurobiological, neuropharmacokinetic and pharmacogenetic aspects of the addiction pathways. Among the three teams of the unit, teams # 1 and 2 are more focused on fundamental research, whereas team # 3 is rather clinically oriented.

Team 1: Neurochemistry and Neurobiology of addictions

During the last four years, this team has focused on four main topics including the interactions between opioid and cannabinoid systems and studies about mechanisms as well as neurochemical and physiological consequences of ecstasy consumption in animal models. As mentioned earlier, publications (31 for 3 publishing scientists, including 10 in 2008) are regular but, since 2004, are only published in journals with median impact factors, except for one paper in 2007 (Neuropsychopharmacology) and a collaborative work in 2006 on the role of the potassium channel TREK-1 in depression-resistant phenotype (Nature Neuroscience).

Future plans include three topics : opiates, cocaine and new treatments. The opiate topic addresses epigenetic modifications induced by morphine in the rat, and integrate the nematode C. elegans model to study behavioural morphological and functional consequences of acute and chronic exposure to morphine. The second topic will also use C. elegans to analyze signalling pathways after acute and chronic cocaine, and study the effect of cocaine on dendritic spines in the rat. Both opiates and cocaine projects will address the question of differential neuroadaptations to chronic drug exposure depending on the mode of drug administration. The last topic aims at establishing gene expression changes profiles in peripheral blood cells in morphine-dependent rats (direct link with the clinic), understanding the neurobiological mechanisms of nitrous oxide (N2O) effects in reducing withdrawal signs among drug addicts, and investigating drug combinatorial approaches for the treatment of addiction.

Strengths of this team are the opportunity to combine neurochemistry and behaviour and to develop new experimental models and approaches. Not only is the overall project extremely well integrated in the research unit program, but also this program is included in the general activity of the IFR "Sciences du Médicament" where number of specialists of different disciplines (from chemistry and mass spectrometry to anatomists and microscopy) are present. Some reservations were made concerning the lack of a general working hypothesis in some aspects of the project. Also, the introduction of operant models such as drug self-administration would be important. Finally, there was also some concern about the adequacy of the C. elegans model in addiction

experiments. Should this model be used, approaches using the power of C. elegans genetics should be developped. Addressing these issues will likely increase the potential of the presently proposed project.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	B	B	A+	A

Team 2 : Neuropharmacokinetics and neurotoxicity of illicit substances and their metabolites. Protecting role of ABC transporters.

The entry into the brain of many compounds, including drugs, is restricted by ATP-binding cassette (ABC) efflux transporters. The blood-brain barrier (BBB) can also be considered as a metabolic barrier because of the expression of drug-metabolizing enzymes in endothelial cells, especially cytochromes P 450 (CYPs).

This team has characterized the ABC transporters and CYP in the human brain as well as the localization of ABC transporters at the rat BBB.

Comparing different data, this team showed that there is a drug-drug interaction between flunitrazepam and buprenorphine which increases the toxic respiratory effects of buprenorpine and may explain the high morbidity clinically observed when both drugs are combined. Moreover, a model was developed to define the toxicokinetics of methadone and its toxicodynamics effects in a clinical case of acute methadone poisonings.

The team leader has an international reputation and the team is one of the most well-recognized among those working on BBB at both European and worldwide level. Also, the team has been instrumental in developing and perfecting the in situ brain perfusion technique which is now used by many other BBB groups worldwide. The notion of BBB heterogeneity is an important focus for this team. Future plans include also identification of transporters involved in organic cation influx into the rodent brain. The team would also like to study effects of cannabinoïds on the expression and function of BBB markers in the rat as well as the modulation of transporters (induction of P-gp at the BBB) by morphine will be investigated from the perspective of a particular cerebro-vascular vulnerability. Moreover, the arrival of the neuroimaging team (presently working in SHFJ-CEA at Orsay) will undoubtedly increase the strength of this team. Among the weaknesses, cellular imaging and cell biology were noted as potentially improvable.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A+	A

Team 3 : Variability of the response to psychoactive substances: intra- and interindividual factors.

The team is divided into two groups, the first one "Clinical and Therapeutic research on addictive behaviours" conducts research studies aimed at describing clinical, pharmacological and genetic variability of addictive behaviours in Humans. This group is highly involved in outpatient programs for opiate dependent individuals on maintenance treatments or cannabis consumers (Lariboisiere Hospital). This group is actively working on large

epidemiological studies on general population in the field of addiction with international collaborations (Barcelona, Spain and also with the University of Michigan, USA). Characteristics of addictive behavior with the potential infuence of psychiatric comorbidity were also examined. Finally, promising results of an open trial testing the therapeutic effects of the antipsychotic drug aripiprazole in cocaine-dependent patients were presented.

The second group "Clinical and experimental toxicology of addictive compounds" has also, as team # 2, worked on the respiratory effects of buprenorphine alone or in association with, benzodiazepines. Effects of methadone and cannabis at high doses were also studied.

The team leader has also a good international recognition and is a member of a substantial number of national and international advisory boards (Drug group at the French agency for the safety and security of health products (Afssaps), EMEA, Association of European psychiatrists). The team has published many papers these past four years (76 "ACL" between 2005-2008) in journals with median impact factors; it can however be noted two recent (2007-2008) papers being published in British Journal of Psychiatry or Plos Med with at least 20 co-authors, indicating an efficient inclusion and participation in collaborative studies.

Future projects are in line with the general interest developed these past four years such as clinical phenotyping, pharmacological trial and studies concerned with Public Health. In relation to the new availability in the unit of specialized equipment pharmacogenomics studies for acute poisoning or deleterious side-effects due to drug will be developed. Cohorts established by the team are unique, and therefore of high interest in the field. Genetic studies may take more davantage of this aspect and broaden both interactions with other cohorts and the set of genes under study.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	B	A

5 • Appreciation of resources and of the life of the research unit

Because of the dissemination of the unit in three relatively far locations, it is difficult to determine the adequacy of the surface for labs and offices (508 m2 at the Faculty of Pharmacy, 352 m2 at hopital F. Widal and 115 m2 at Orsay). The space and the organization depend on the location. Interviews with the University Representatives of Paris 5 indicated that a future program that gathers different pharmaceutical labs, including the Inserm U705 unit, in the Faculty of Pharmacy, Avenue de l'Observatoire in Paris should be voted in few days (feb 2009). This new organization, however, will not be functional in the next four years. Finally, the unit can take advantage of its association in the IFR "Sciences du Médicament" and has no equipment problem such as confocal microscopy, mass spectrometry or PET imaging at SHFJ at Orsay.

Financial resources have increased regularly in the four past years (from 274 to 489 kEuros) with contracts from the industry (8) or the public (MILDT, 4), although the financial support from ANR remains modest. All three teams are affiliated to the Doctoral School of Drugs from University Paris Descartes and, as mentioned above, the great majority of scientists of this unit are also university teachers in basic neuroscience and addiction courses. The throughput of PhD theses has been steady, and the new doctors have found appropriate postdoc positions within the pharmaceutical industry.

6 • Recommendations and advice

— Strong points :

A coherent unit with one main scientific goal focused on addiction. The unit is also internally diverse, from preclinical to clinical and epidemiological studies, which facilitates integrative and translational medicine.

The integration of a neuroimaging group into the unit.

Significant involvement in societal planning for reducing drug consumption.

— Weak points :

Scientific articles should have more impact, which is part of future goals of principal investigators.

Dissemination of the unit into three sites.

— Recommendations :

There is a need for higher impact publications which, together with cutting edge findings that will emerge from the program, may necessitate a more aggressive publication policy.

If possible, have more frequent lab meetings, eventually two teams together instead of three, to improve even more the coherence of the unit.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 30 mars 2009

DRED 09/n°107

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
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Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport de comité de visite concernant l'unité « **UM 39 Neuropsychopharmacologie des addictions : Vulnérabilité et variabilité expérimentale et clinique** » rattachée à mon établissement.

L'Université a pris bonne note des remarques du comité de visite et veillera, en partenariat avec l'INSERM et le CNRS, à ce que les recommandations faites soient suivies d'effet.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

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Fichier 2

Comments

We appreciate that the visiting committee has underlined the dynamism of the unit “full of positive energy”, “open scientific discussion” “solid publication record on addiction” and the relevance of the integration of EA3621 and a neuroimaging group of CEA within the 3 actual teams for the next 4 years. Moreover one of our main challenge at the creation of the unit was to develop “a coherent unit with one main scientific goal focused on addiction” with “integrative and translational” programs, which has been achieved. We agree with the evoked weak points and recommendations. We can add the following comments:

1 - Dissemination of the unit in 3 relatively far locations.

The third and new location corresponds to the neuroimaging group which has to be localized on the site of the cyclotron and PET camera in Orsay. The second location which is close from the faculty of Pharmacy is based in F. Widal-Lariboisière Hôpital to allow clinical studies which facilitates the development of integrative and translational medicine, one principal goal of the unit.

Finally, the main site of the Faculty of Pharmacy will benefit of a new area of 600 m^2 allowing unit members to work in the same space as members of EA3621.

The visiting committee reports that “this new organization will not be functional in the next four years”. This statement is not exact as the relocalization process of the unit will occur in 2009/2010 (fundings were given by Paris Descartes University).

2 - Need for higher impact publications and cutting edge findings

We agree to develop a more aggressive publication policy, together with more international scientific collaborations. As explained to the visiting committee, this first “4-years program” was devoted to allow unit members to develop integrative and translational programs from preclinical to clinical studies and associating as more as possible the 3 teams.

We are convinced that some of our programs which are now running will provide cutting edge findings and help to reach highest profile publications.

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Team 1: specific comments

We are pleased that the visiting committee emphasizes that “our overall project is very very well integrated in the research unit program” and “ in the “general activity of the IFR”.

As the committee also notes, “strenghts of our team are the opportunity to combine neurochemistry and behaviour and to develop new experimental models and approaches” . To gain these objectives, the team is working at the interface of different disciplines, not only “Neuroscience”. Thus, several papers have also been published in the best journals of *Toxicology* (Toxicology and Applied Pharmacology; IF: 3.8, rank 5 on 73 journals in this discipline), *Chemistry* (Curr. Top. Med. Chem., IF: 4.3, rank 5 on 41 journals in this discipline), *Pharmacology* (Br. J. Pharmacol, IF: 3.8, rank 39 on 205 journals in this discipline), *Anaesthesiology* (Pain, IF: 5.2, rank 1 on 22 in this discipline), or *Clinical Neurology* (Pain and Int. J. Neuropsychopharmacol, IF: 5.2 and 4.9, respectively; ranks 11 and 12 on 146 journals in this discipline). As mentioned by the visiting committee we have also good papers in the field “Neuroscience” (Neuropsychopharmacology, Nat. Neurosci) and globally most (70%) of the papers of the team are published in journals ranking in the first third of journals referenced in the different fields. We’ll pursue and amplify our policy of publication in the higher rank journals during the next four years.

The general strategy of all our projects is to establish a continuum from behavioural studies and biological mechanisms. Among these projects most of them have a strong background, and correspond to hypotheses already well described in the literature. However, as there is consensus that addict patients are not efficiently treated currently, we also believe that one of our missions is to develop innovative projects. These projects are certainly more risky, but could lead to cutting-edge findings, with the discovery of new mechanisms not at all investigated today.

Addiction is a complex human pathology that we cannot reduce to an animal model (e.g. rodents or worms). Obviously, the *C. elegans* model, is not *per se* a model of addiction. However, we believe that this animal model is a powerful model for the study of many biological processes using the power of its genetics, as we stressed. It possesses a simple nervous system with known anatomy and connectivity, allowing investigation of the signalling pathways involved in the neuroadaptations following drug exposure. Moreover *C. elegans* can be used to characterize known genes as well as to identify new genes regulating responses to drugs of abuse. Since 2000, 15 articles have been published in our field of interest with this model, with some of them in the best journals (Neuron, Cell, JBC, EMBO J.) We believe that the development of this model with the arrival of two new researchers experienced in this field in the team will lead us to develop projects with an important impact. This new approach is ambitious but will undeniably enlarge the potential of our general strategy of behavioural and molecular studies.

Team 2: specific comments

Team 2 is aware of building its scientific strategy on the use of translational approaches to raise cutting edge findings in the domain of blood-brain barrier research. As recognized by the visiting committee, the integration of CEA neuroimaging group will increase the strength of the team. Moreover, the integration of one scientist from EA 3621, who is also in charge of the cellular imaging platform of IFR71, will help to cancel our relative weaknesses in the field of cellular imaging and cell biology.

Professor Jean-Michel Scherrmann
Paris, April 2, 2009

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