EPTRI

European Paediatric Translational Research Infrastructure

WP7 - Thematic platform Developmental Pharmacology

Feasibility study on the systematic use of placental platforms: Melatonin as a neuroprotective agent

Evelyne Jacqz-Aigrain – APHP

EPTRI Stakeholders Roundtable – July 9th ,2020

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 777554

Melatonin Feasibility Study

Title of the study:

Melatonin administered during pregnancy as a potential neuroprotective agent against neonatal brain damage

The study proposal was submitted responding to the EPTRI call for FSs launched on 14 June 2019

Presenter(s):

Evelyne Jacqz-Agrain, Valery Elie

Background

Fetal brain injury has multiple causes

- Prematurity : *most significant risk factor*
- **Frequent complication** *of hypoxia, haemorrhage, infections etc.*

Resulting in high morbidity associated with

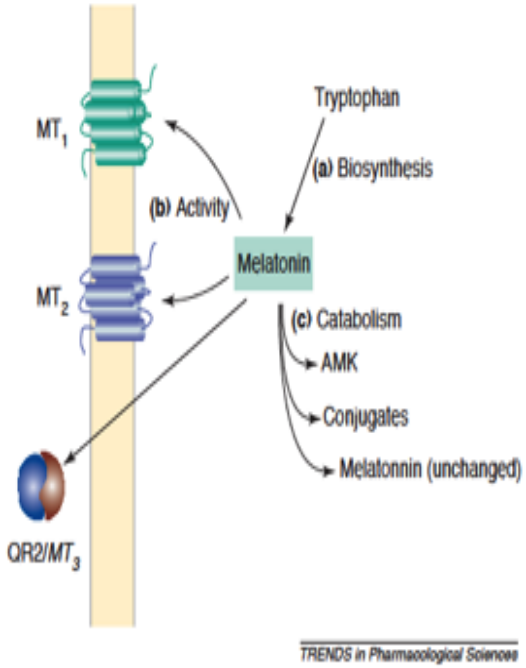
- Lifelong motor, sensitive and cognitive dysfunction
- Long-term impact depends on: *GA, duration & severity of the event*

Researches aim to reduce impact and validate prevention

- Multiple strategies: *therapeutic hypothermia, delayed umbilical cord clamping etc.*

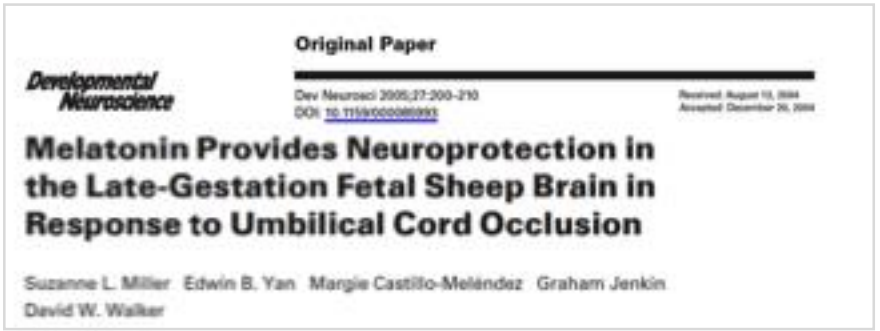
Melatonin

- Pineal hormone (hypothalamus)
- Specific receptors MT1-2
- Anti-inflammatory properties
- Protective effects against oxydative Stress
- Placental synthesis
  - Excellent biosafety profile
  - Easily crosses the placenta and blood–brain barrier



Good candidate for the management of fetal/neonatal OS-related disorders

Melatonin in animal experiments



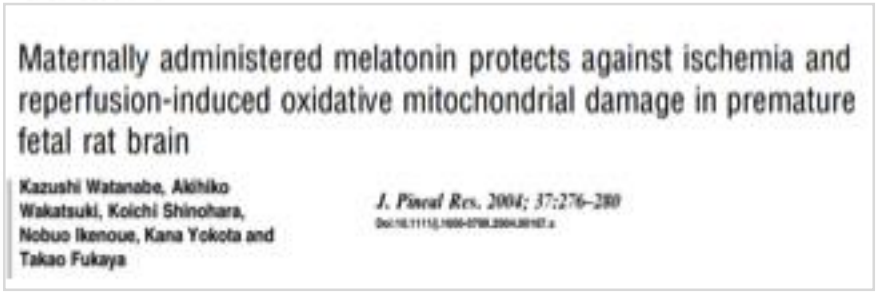
Original Paper

Developmental Neuroscience

Dev Neurosci 2005;27:200–210
DOI: 10.1159/000086993

Melatonin Provides Neuroprotection in the Late-Gestation Fetal Sheep Brain in Response to Umbilical Cord Occlusion

Suzanne L. Miller Edwin B. Yan Margie Castillo-Meléndez Graham Jenkin David W. Walker



Maternally administered melatonin protects against ischemia and reperfusion-induced oxidative mitochondrial damage in premature fetal rat brain

Kazushi Watanabe, Akihiko Wakatsuki, Koichi Shinohara, Nobuo Ikenoue, Kana Yokota and Takao Fukaya

J. Pineal Res. 2004; 37:276–280

Contents lists available at ScienceDirect

Pharmacological Research

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

Melatonin improves short and long-term neurobehavioral deficits and attenuates hippocampal impairments after hypoxia in neonatal mice

Zhen Wang, Dexiang Liu, Jingmin Zhan, Kai Xie, Xueer Wang, Xiuying Xian, Jianhua Gu, Wenqiang Chen, Aijun Hao

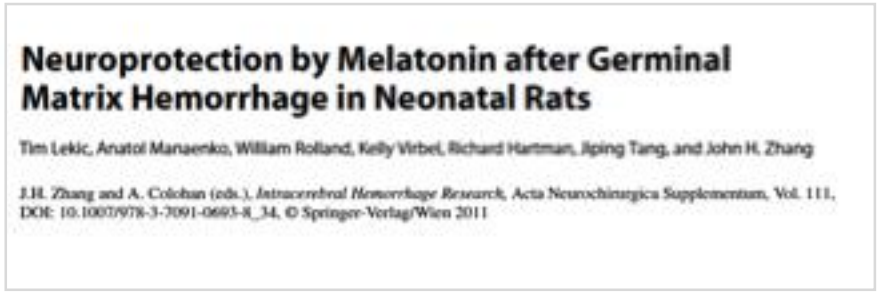
Original Paper

Developmental Neuroscience

Dev Neurosci 2009;31:437–451
DOI: 10.1159/000232562

Neuroprotective Properties of Melatonin in a Model of Birth Asphyxia in the Spiny Mouse *(Acomys cahirinus)*

Lisa C. Hutton, Mahila Abbass, Hayley Dickinson, Zoe Ireland, David W. Walker



Neuroprotection by Melatonin after Germinal Matrix Hemorrhage in Neonatal Rats

Tim Lekic, Anatol Manaenko, William Rolland, Kelly Virbel, Richard Hartman, Jiping Tang, and John H. Zhang

J.H. Zhang and A. Colohan (eds.), *Intracerebral Hemorrhage Research*, Acta Neurochirurgica Supplementum, Vol. 111,
DOI: 10.1007/978-3-7091-0693-8_34, © Springer-Verlag/Wien 2011

Original Paper

Neonatology

Neonatology 2010;98:33–40
DOI: 10.1159/000264205

Therapeutic Effects of Maternal Melatonin Administration on Ischemia/Reperfusion-Induced Oxidative Cerebral Damage in Neonatal Rats

Fumiaki Hamada, Kazushi Watanabe, Akihiko Wakatsuki, Ryuhei Nagai, Koichi Shinohara, Yoshihiro Hayashi, Rina Imamura, Takao Fukaya

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Pre-clinical evidence of Melatonin neuroprotective effect

AIM of the Melatonin FS

AIM of the Feasibility Study to be conduct in EPTRI was:

- **to test the potentiality of EPTRI to provide innovative research services to conduct the proposed Melatonin study.**

Taking into account the study:

- **Objectives**
- **Methodology**
- **Services needed**
- **Timing and costs**

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Objectives

- Evaluate the neuroprotective effect of melatonin in **preterm neonates** when administered to the **mother during** (e.g. premature labour, preeclampsia, etc) **or prior to foetal distress** using **pre-clinical models and "translational data on the physiology of melatonin during normal and complicated pregnancies.**

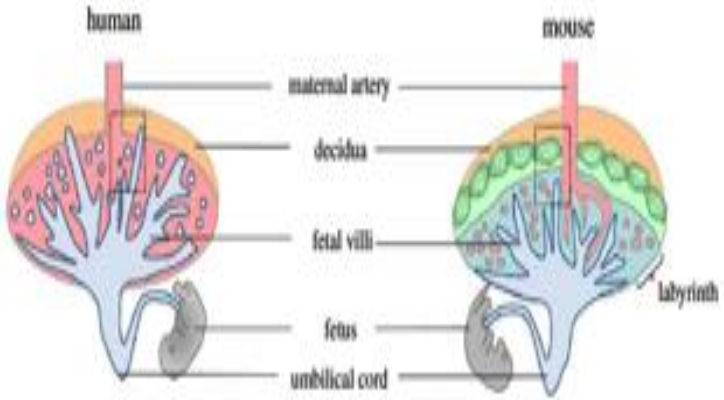
- New innovative data to **predict placental metabolism** and **transfer to the foetus,** as well as foetus disposition, efficacy and safety may provide important information that may influence drug dosage and administration of drugs already marketed and new drugs to be developed

Methodologies

- **Animal studies:**

Determine melatonin concentrations in maternal and foetal plasma, placenta, and foetal brain and its safety profile

Determine melatonin pharmacodynamics in a developing organism



- **Select the appropriate model(s)**

Similar physiology and biological functions (placenta/juvenile animal)

Hemochorial placenta: rat, mouse

Juvenile animal: similar development

Foetal and neonatal exposure evaluation: same animal model ?

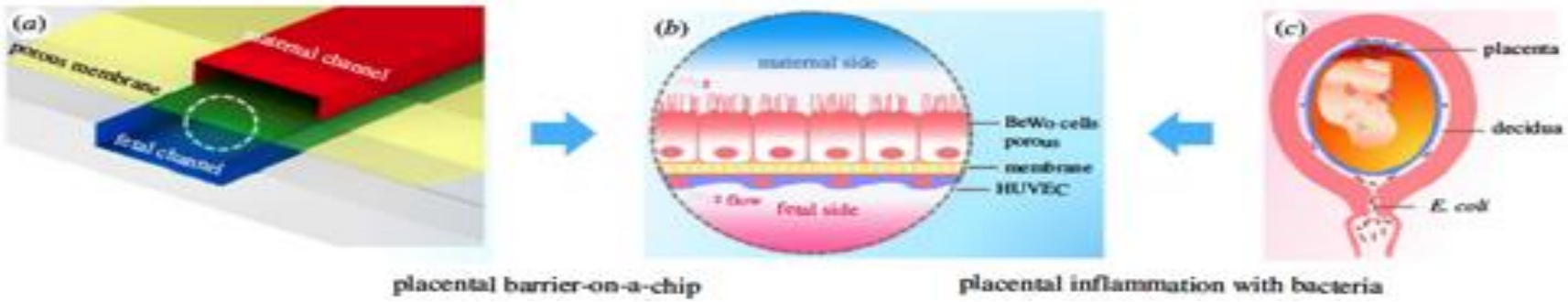
Long-term follow-up: adapted tools for animals ?

Methodologies

Placenta-on-a-chip:

- Micro-fluidic device
- In-vitro setting mimicking placental function (endothelial + trophoblast cells)
- Practical model, smallest budget, large number of applications (incl. infection)

→ **Promising but recent approach – next steps needed to improve the fabrication process and validate the system**



placental barrier-on-a-chip

placental inflammation with bacteria

(Pemathilaka et al. 2019)

Methodologies

Scientific and technical development

- Expertise needed at each step of the research
- Large panel of techniques required : pathology, analytics (spectro/electro-analytical, HPLC), molecular biology…)
- **Validation and control are crucial**

Pharmacometrics and Bioinformatics

- Modelling and simulation: PBPK, PKPD, extrapolation (animal, in-vitro, ex-vivo data)

Feasibility study process

After the proposal application, a multi-step procedure has been foreseen

Step 1 : Advisory Board Assessment

The EPTRI AB assessed the proposal according to a predefined Assessment Report Form. A Rapporteur and a Co-rapporteur prepared the assessment for the final approval

	Summary of AB opinion	Final comments for further implementation
EPTRI mission and abilities	The proposal meets EPTRI mission and abilities with special reference to: a) Platform 3. **Developmental pharmacology** c) **Centralised services**	
Scientific contents (Excellence)	The proposal has been judged excellent. The main contributions to EPTRI valorisation could be: 1. Valorisation of many preclinical, ex-vivo research, needed to perform a paediatric drug developmental plan. (through Placenta Platform); 2. Application of laboratory methodologies specifically developed for paediatric research (small sample, drug disposition methods specifically developed for children); 3. Suggestions on how translate in a future clinical setting of the main results (translational relevance); 4. Capacity to attract funds and new users.	

STEP 2 : Advisory Board Recommandations

	Summary of AB opinion released on 15/01/2020	Final comments for further implementation
Services and facilities required	Contribution needed from EPTRI has **been identified in the proposal.** 1. Animal pregnancy models to study maternal and fetal efficacy/disposition and safety 2. Human in vivo data during healthy pregnancy and during disease complicated pregnancies 3. Potential impact of covariates on drug disposition in the foeto-maternal unit 4. Pharmacokinetics and PBPK approaches to mechanistically elucidate druf exposure like melatonin in fetal brain (pre-clinical models) 5. Small volume sample analytical assays 6. In vitro cell-based models to assess placental transport and functionality	- Potentially the requested competencies could be identified in Platform 3 - Translation of the results into a clinical developmental phase should be taken into consideration.

Step 3 : Report on services availability

The EPTRI coordinator required 1) the FS proposer to provide more details on the proposal and 2) the " Melatonin Feasibility Study preparation Expert Group" to proceed with the identification of suitable providers of the services

A coordination group has been set up (WP2 and WP9 and EPTRI TRP Developmental Pharmacology) with the aims:

- To identify **which RUs** within EPTRI are potentially able to meet the users requests
- To specify the **interest of the service** in the context of a paediatric medicine developmental process and to bridge with representative in EPTRI of paediatric **clinical initiatives**

Identification of RUs and other services within EPTRI:

Service required	N° of RUs identified
Pharmacokinetics and PBPK approaches to mechanistically elucidate drug exposure like melatonin in foetal brain (pre-clinical models)	5
Animal pregnancy models for related changes in disposition of systemically administered melatonin	2
Animal models for safety and efficacy studies	2
In vitro cell-based models to assess placental transport and functionality (placenta on a chip)	2
Small volume sample analytical assays	1

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Report on services availability

Other services in EPTRI have been identified at central level:

- Activation of contacts with paediatric clinical initiatives
- Scouting of funding opportunities.
- Ethical and regulatory support

Conclusions

- **MelBrain feasibility study** was proposed by investigators involved in pregnancy research and pregnancy care to test the potentiality of EPTRI to provide innovative research service in this field.
- **EPTRI identified 8 research units** in 6 European countries, able to provide 5 required services.
- The propose study identified a **very innovative research need** dealing with placental and neonatal studies that the **EPTRI placenta platform** that is part of the TRP Developmental Pharmacology has **experts and research units capable to answer this specific need.**

Thank you!