BOOK OF ABSTRACTS

EDSAT
ANNUAL MEETING 2023

24 March 2023
MADRID

SÍNDROME DE DRAVET
FUNDACIÓN

ORGANISING COMMITTEE

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SUMMARY

After the success of the first edition, Dravet Syndrome Foundation Spain and the European Dravet Syndrome Advanced Therapies Working Group (EDSAT) are delighted to organise the second edition of the **European Dravet Syndrome Advanced Therapies (EDSAT) Meeting**, a one-day networking event satellite to the Dravet Syndrome Conference 2023.

This **international** meeting is taking place **in person** on **Friday 24th of March 2023 in Madrid, Spain**. The EDSAT Meeting will provide the latest updates on the **Advanced Therapies in Medicinal Products (ATMPs) for Dravet syndrome**. In addition, attendees will have the unique opportunity to **exchange ideas** and **foster collaborations** with **key scientists and guest** industry, clinical and regulatory **experts in product and clinical development**.

The **registration is free of charge**, but **mandatory** for organisational reasons. Registration also includes **free access** to the **networking dinner**, in the evening of March 23rd, 2023. However, to maximise networking opportunities, this event is **limited to 50 attendees**, who will be processed on a first-come, first-served basis. To encourage participation of usually **underrepresented countries** in Europe, **travel grants** will be offered to students and postdocs coming from those countries. The EDSAT Meeting will be open to students, early career scientists, leading investigators, policy makers and other professionals from the pharmaceutical and healthcare sector with the common goal of promoting Dravet syndrome research and patient access to ATMPs.

The **EDSAT Meeting 2023** will take place at the **Official College of Nursing of Madrid** (Spain), located in the former factory of the American sewing machine company Singer, an emblematic building of the 20th century.

Breaks and lunch will take place in the **Nursing History Museum** of the Official College of Nursing in Madrid, which is the only nursing museum in all of Spain, receiving visitors from all over the world.

Registration is **free of charge**, but mandatory for organisational reasons.



Hall and museum of the Illustrious Official College of Nursing of Madrid (Spain)

WHAT IS DRAVET SYNDROME?

Dravet syndrome (DS), also known as Severe Myoclonic Epilepsy in Infancy, is a **rare and severe developmental and epileptic encephalopathy** affecting 1 in 16'000 live births.

In more than 80% of patients, Dravet syndrome is caused by a ***de novo* pathogenic variant in the *SCN1A* gene**. These mutations result **in** the reduction of the voltage-gated sodium channel subunit Nav1.1. Variants in other genes such as *GABRG2*, *GABRA1* or *STXBP1* have also been linked to Dravet syndrome.

DS is characterised by a **drug-resistant epilepsy**, and by a number or severe **comorbidities**. Among these there are **cognitive, psychomotor and language impairment, as well as behavioural disorders**.

The first symptom of Dravet syndrome is typically a convulsive seizure appearing in the first year of life, in a previously healthy child. Further **seizures are frequent and often prolonged**, sometimes evolving into **status epilepticus**, although the seizure types depend on age.

During the second year of life, the **neurodevelopmental impairment** becomes evident. **Secondary conditions** such as sleep disturbances, growth and eating difficulties, and frequent respiratory tract infections are shared by almost all Dravet syndrome patients.

Dravet syndrome has a **15% mortality rate**, with 50% of cases due to **SUDEP** (Sudden Unexplained Death in Epilepsy).

Will you help us to find a cure for Dravet syndrome?

More information about Dravet syndrome can be found on our website here: https://www.dravetfoundation.eu/sobre-dravet/ (click "Translate" at the bottom-right corner to get the English version).

ABOUT THE EDSAT WORKING GROUP

In November 2020, Dravet Syndrome Foundation Spain launched **a pioneer initiative** to bring together European experts in ATMPs for Dravet syndrome, the European Dravet Syndrome Advanced Therapies (EDSAT) Working Group. Through a scientific and multidisciplinary forum **focused on collaboration and cooperation**, this initiative aims at removing research barriers between institutions **to advance fundamental and translational science in ATMPs for Dravet syndrome**.

This will be the second time that representatives of the **main European groups** working on ATMPs for Dravet syndrome are brought physically together in a framework of collaboration. Importantly, this represents also a unique and uncommon initiative, since it is coordinated **by a patient advocacy organisation**.

The EDSAT is currently formed by the team led by the following Principal Investigators: **Dr Vania Broccoli** (San Raffaele Scientific Institute, IT), **Dr Massimo Mantegazza** (Institute of Molecular and Cellular Pharmacology [IPMC], FR), **Prof Moran Rubinstein** (Goldschleger Eye Research Institute, IL), **Dr Rubén Hernández-Alcoceba** (Center for Applied Medical Research [CIMA], ES), **Dr Gabriele Lignani** (UCL Institute of Neurology, UK), **Dr Rajvinder Karda** (EGA Institute for Women's Health, UK), **Dr Carlos Romá-Mateo** (University of Valencia, ES), **Prof Heidrun Potschka** (Ludwig-Maximilians-University Munich, DE) and **Prof Else Tolner** (Leiden University Medical Center, NL). The group is coordinated and facilitated by **Dravet Syndrome Foundation Spain,** and it is always **open** to incorporating **new members**.

Dravet Syndrome Foundation Spain is a non-profit organisation, established in 2011, that **promotes, encourages, and connects the world's leading research centres for Dravet syndrome** and related diseases. It supports **patients** and their **families** by providing, among others, with **economic and psychosocial support**. In recognition of our work, Dravet Syndrome Foundation Spain has received numerous awards and honours, including the **Epilepsy Award from the Spanish Society of Neurology**. To learn more about **Dravet Syndrome Foundation Spain**, please visit our website at www.dravetfoundation.eu.

AGENDA 2023

TIME	TITLE
08.30 - 09.00	**Welcome & Registration**
09.00 - 09.10	**Opening Statements & Introduction to the program** *Jose Ángel Aibar, Dravet Syndrome Foundation Spain*
09.10 - 09.55	**Research Talk Session I**
09.10 - 09.25	**Targeting GABA-switch can rescue behavioural defects but not seizures in Scn1a+/- DS mice** *Massimo Mantegazza, Côte d'Azur University & CNRS*
09.25 - 09.40	**Validation of θ-γ PAC as potential EEG biomarker to assess efficacy of the anti-seizure treatment** *Else A. Tolner, Leiden University Medical Center*
09.40 - 09.55	**Boosting a homeostatic response as therapeutic approach in Scn1a+/- Dravet syndrome mice** *Evgeniia Rusina, Institute of Molecular and Cellular Pharmacology, CNRS*
09.55 - 10.40	**Workshop 1: Existing ASMs for Dravet Syndrome and related epilepsies**
09.55 - 10.15	**Introduction to existing ASMs for Dravet Syndrome and related epilepsies** *Heidrun Potschka, Ludwig-Maximilians-University Munich (GE)*
10.15 - 10.30	**Dynamic Group Discussion on existing ASMs for Dravet Syndrome and related epilepsies** *All attendees*
10.30 - 10.40	**Pooling of Ideas/ Conclusions** *EDSAT Group leaders*
10.40 - 11.00	**Poster Session & Networking Coffee Break**
11.00 - 11.30	**Research Talk Session II**
11.00 - 11.10	**Strategies to reduce inflammation of adenoviral vectors in a Dravet syndrome mouse model** *Rubén Hernández, CIMA Universidad de Navarra*
11.10 - 11.20	**Constitutive restoration of Nav1.1 levels in GABAergic neurons ameliorates DS phenotype** *Martina Mainardi, San Raffaele Scientific Institute*
11.30 - 12.30	**Workshop 2: Pros and cons of the different advanced therapy strategies for Dravet syndrome**
11.30 - 11.45	**Introduction to the pros and cons of the different advanced therapy strategies for Dravet syndrome** *Gabriele Lignani, UCL Queen Square Institute of Neurology & Rubén Hernández, CIMA Universidad de Navarra*
11.45 - 12.15	**Dynamic Group Discussion on the pros and cons of the different advanced therapy strategies for Dravet syndrome** *All attendees*
12.15 - 12.30	**Pooling of Ideas & Conclusions** *EDSAT Group leaders*
12.30 - 14.00	**Poster Session & Networking Lunch**
14.00 - 14.45	**Expert Panel: New insights into the neuropathopsychology of Dravet syndrome** *Massimo Mantegazza, Cote d'Azur University & CNRS*
14.00 - 14.10	**Initial pathological mechanism and remodelling (secondary modifications)** *Massimo Mantegazza, Cote d'Azur University & CNRS*
14.10 - 14.20	**Secondary modifications studied with proteomics and metabolomics** *Heidrun Potschka, Ludwig-Maximilians-University Munich*
14.20 - 14.30	**Can upregulation of Nav1.1 overcome secondary modifications?** *Gaia Colasante, San Raffaele Scientific Institute*
14.30 - 14.35	**Open discussion on the topic** *Sarah Weckhuysen, University of Antwerp*
14.35 - 14.45	**Dynamic group discussion** *Speakers and attendees*
14.45 - 15.15	**Poster Session & Networking Coffee Break**
15.15 - 15.45	**Research Talk Session III**
15.15 - 15.30	**A human cortical assembloid model of Dravet Syndrome** *Clara Zourray, UCL Queen Square Institute of Neurology*
15.30 - 15.45	**Sleep and temperature dysregulation in a Dravet syndrome mouse model** *Saja Fadila, Tel Aviv University*
15.45 – 16.00	**Local reactivation of Scn1a gene in a reversible mouse model of DS** *Gaia Colasante, San Raffaele Scientific Institute*
16.00	**Closing Remarks & Thank-yous** *José Ángel Aibar, Dravet Syndrome Foundation Spain*

Please note that there will be a networking dinner on the evening before the event and visit www.dravetconference.com for the up-to-date agenda.

ORAL PRESENTATIONS ABSTRACTS

(in order of presentation)

Targeting GABA-switch can rescue behavioural defects but not seizures in Scn1a+/- Dravet Syndrome mice

ORAL AND POSTER PRESENTATION

Lara Pizzamiglio[1,2], Fabrizio Capitano[1,2], Giuliana Fossati[3], Elisabetta Menna[3,4], Isabelle Léna[1,2], Flavia Antonucci[4,5], Massimo Mantegazza[1,2,6]

[1]Université Côte d'Azur, Institute of Molecular and Cellular Pharmacology (IPMC), Valbonne-Sophia Antipolis, France.
[2]CNRS UMR7275, Institute of Molecular and Cellular Pharmacology (IPMC), Valbonne-Sophia Antipolis, France.
[3]IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy.
[4]Institute of Neuroscience - National Research Council of Italy (CNR) c/o Humanitas Mirasole S.p.A, Rozzano, Milan, Italy.
[5]Department of Biotechnology and Translational Medicine, University of Milan, Milan, Italy.
[6]Inserm, Valbonne-Sophia Antipolis, France.

Abstract text: We investigated neurodevelopmental defects in Dravet syndrome (DS) Scn1a+/- mice before seizure onset (post-natal day, P, 20-21) and assessed their impact on epileptic and behavioural phenotypes performing specific pharmacological interventions. We evaluated in vivo features performing behavioural tests and cellular/network properties performing ex-vivo electrophysiological recordings.

We show that, well before seizure onset, Scn1a+/- mice display early behavioural defects and delayed neurodevelopmental milestones, such as eye opening and GABA-switch. This is consistent with a reduction of GABAergic synaptic transmission directly caused by the Scn1a mutation, which we have observed already at P11-12. Furthermore, we assessed the importance of this developmental delay as pathological mechanism in Scn1a+/- mice rescuing GABA-switch by targeting either KCC2 or NKCC1 with the drugs KU55933 (KU) or bumetanide, respectively.

Both drugs rescued social interaction deficits and reduced hyperactivity observed in P21 Scn1a+/- mice. Bumetanide also improved spatial working memory deficit. Notably, neither KU nor bumetanide had effect on seizures or mortality rate.

Our results highlight neurodevelopmental components in DS that selectively underlie autistic-like behavioural defects but not seizures, and provide evidence to the hypothesis that seizures and neuropsychiatric dysfunctions can be uncoupled in DEEs and should be treated separately with a targeted pharmacological strategy.

NOTES

Validation of θ-γ PAC as potential EEG biomarker to assess efficacy of the anti-seizure treatment

Georgii Krivoshein[1], Arn M.J.M van den Maagdenberg[1,2], Else A. Tolner[1,2]

[1]Department of Human Genetics, Leiden University Medical Center, Leiden.
[2]Department of Neurology, Leiden University Medical Center, Leiden.

ORAL AND POSTER PRESENTATION

Abstract text: Variable responsivity to anti-epileptic drugs (AEDs) in Dravet Syndrome (DS) patients may relate to variability in the extent of neuronal network disinhibition. A functional biomarker reflecting the extent of disinhibition could help select AEDs that effectively suppress attacks. Hippocampal inhibitory networks contribute to 'phase-amplitude coupling' (PAC) between theta (θ) and gamma (γ) oscillations, measurable by EEG. DS mice were shown to display impaired θ-γ PAC, resulting of disinhibition. We here validate EEG θ-γ PAC as marker to assess efficacy of AEDs.

The scn1a KO mouse model of DS was used to record continuous cortical and hippocampal EEG. Suitability of θ-γ PAC as an indicator of drug efficacy was tested by acute administration of AEDs known to enhance neuronal inhibition, cannabidiol (CBD), and with adverse effects (possibly by enhancing inhibition), carbamazepine (CBZ). θ-γ PAC was calculated up to 5 h following drug/vehicle by a modulation index metric from seizure-free REM sleep epochs. Anti-seizure drug effects were assessed on hyperthermic seizure threshold.

Our data indicate that CBD restores impaired θ-γ PAC in DS mice, whereas CBZ does not. In conclusion, θ-γ PAC has potential to assess efficacy of AEDs. Ongoing studies assess the relationship with anti-seizure effects and include tests with additional and novel AEDs. Parallel analysis of clinical depth EEG during AEDs tapering help validate θ-γ PAC for clinical use.

NOTES

Boosting a homeostatic response as therapeutic approach in Scn1a+/- Dravet Syndrome mice

Evgeniia Rusina[1,2], Paolo Scalmani[3], Fabrizio Capitano[1,2], Fabrice Duprat[1,2,4], Isabelle Lena[1,2], Massimo Mantegazza[1,2,4]

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ORAL AND POSTER PRESENTATION

Abstract text: Dravet Syndrome (DS) is a severe developmental encephalopathy resulting in intractable epileptic seizures and associated with multiple comorbidities such as cognitive deficits, social impairment, motor dysfunction, affective problems, and sleep disturbances. We have identified a homeostatic response in the Scn1a+/- mouse model of Dravet syndrome (DS), in which the peptidic neuromodulator cholecystokinin (CCK) is involved and that we are boosting as a therapeutic approach.

In fact, we performed chronic intranasal administrations of CCK to investigate its effect on both seizures and behavioural abnormalities. First, we have tested the effect of CCK on hyperthermic seizure induction and we found an increase of seizure threshold, positively correlated with the dose. In a separate series of experiments, we evaluated the effect of chronic CCK treatment on spontaneous seizures. We observed a significant reduction in spontaneous seizure frequency in the CCK-treated mice, compared to the vehicle-treated controls.

Subsequently, we performed a battery of behavioural tests on a different cohort of juvenile mice that underwent chronic CCK treatment. We have found no significant effect on hyperactivity or anxiety, but a rescue of sociability and memory dysfunctions. Importantly, we have not observed any adverse effects of CCK. Overall, CCK may be a therapeutic approach in DS.

NOTES

Strategies to reduce inflammation of adenoviral vectors in a Dravet Syndrome mouse model

Ana Ricobaraza[1], María Buñuales[1], Manuela Gonzalez[1], Rocío Sanchez-Carpintero[2], Rubén Hernandez-Alcoceba[1]

[1]Gene Therapy Program. CIMA. University of Navarra. Pamplona, Spain.
[2]University Clinic of Navarra. Dravet Syndrome Unit. Pediatric Neurology Unit. IdiSNA, Navarra Institute for Health Research. Pamplona, Spain.

ORAL AND POSTER PRESENTATION

Abstract text: Gene supplementation of SCN1A is challenging because the coding sequence is large (6 Kb) and prone to re-arrangements. We have provided proof of concept that High-Capacity Adenoviral vectors (HC-AdV) can deliver the full SCN1A cDNA to the brain of a DS mouse model and achieve disease amelioration. However, inflammation is one of the main concerns related to this type of vectors. We have explored different strategies to overcome this potential problem.

On one side, we modified the capsid of human adenovirus type 5 in order to reduce binding to scavenger receptors (SR) in macrophages and microglia. To this end, we substituted the hypervariable regions in the capsid protein hexon by equivalent regions from adenovirus type 6, which shows low SR binding. On the other side, we developed a shielding polypeptide based on anti-hexon monoclonal antibodies. Only the capsid modification was able to reduce infection of primary astroglial cells. However, both strategies impaired the infection of target cells in vitro (inhibitory GABAergic neurons), and reduced neuronal transduction in vivo.

In contrast, we found that a short corticosteroid treatment (dexamethasone) is able to diminish the adenovirus-related inflammatory response in mice without significant reduction of transduction efficacy. Our results favour the use of prophylactic corticosteroids in gene therapy protocols involving adenoviral vectors.

NOTES

Constitutive restoration of Nav1.1 levels in GABAergic neurons ameliorates Dravet Syndrome phenotype

Martina Mainardi[1], Claudia Di Berardino[1], Vania Broccoli[1,2], Gaia Colasante[1]

[1]Stem Cell and Neurogenesis Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy.
[2]National Research Council (CNR), Institute of Neuroscience, 20129 Milan, Italy.

ORAL AND POSTER PRESENTATION

Abstract text: Dravet Syndrome (DS) is an infantile epileptic encephalopathy associated with high risk of sudden unexpected death (SUDEP), primarily caused by SCN1A gene haploinsufficiency. Extensive studies are ongoing in the field of gene therapy to provide a cure; however, several information is still missing on the contribution of different neuronal populations in DS.

By employing a DS reversible mouse model carrying a floxed STOP cassette that can be conditionally removed (Scn1aStop/+), we restored Nav1.1 expression only in GABAergic interneurons (IN) crossing the Scn1aStop/+ mouse with Gad2-ires-Cre transgenic line.

Scn1aStop/+;Gad2Cre+/- mice were fully protected from SUDEP up to post-natal day 60 and from febrile seizures at the onset of the disease, when IN firing properties appeared normalised. Later during disease progression, mice displayed spontaneous seizures with a trend towards reduced number and frequency in comparison to Scn1aStop/+;Gad2Cre-/- mice. Moreover, seizures appeared milder in severity, and a significant reduced susceptibility to febrile seizures was observed.

These data suggest that constitutive abrogation of Nav1.1 haploinsufficiency in GABAergic INs results in a milder phenotype characterised by less severe spontaneous seizures, and protection from febrile seizures and SUDEP. While further investigation is needed to understand the relevance of different IN subtypes, these data will provide new insights for the optimization of gene therapy delivery.

NOTES

A human cortical assembloid model of Dravet Syndrome

Clara Zourray[1,2,3], Nathanael O'Neill[1], James Street[1], Serena Barral[2,3], Gabriele Lignani[1]

[1]*UCL Institute of Neurology.*
[2]*Zayed Centre for Research.*
[3]*Institute of Child for Health.*

ORAL AND POSTER PRESENTATION

Abstract text: Animal models have been instrumental in advancing our understanding of DS pathogenesis and as preclinical models to test advanced gene therapies. However, important genomic differences in SCN1A regulation between rodents and humans and influences of the genetic background may hinder our ability to effectively translate preclinical findings in rodents onto the clinic. Patient-derived somatic cells can be converted into human iPSCs, capable of differentiating into a variety of cellular lineages.

Leveraging this, the generation of stem-cell derived 3D cell cultures – known as organoids – allows to model brain structures in remarkably complex ways. Cortical assembloids are generated from the fusion of a cortical and a subpallial organoid, which allows the generation of both excitatory and inhibitory cortical neurons and recapitulates the tangential migration of cortical interneurons from the subpallium into the cortex, as seen in vivo. Importantly, we have observed Nav1.1 expression at later stages of development in this model.

Therefore, we generated iPSC lines from three Dravet patients and corrected two of them using CRISPR. Using a protocol we have established to record evoked epileptiform activity in mature assembloids, we have observed for the first time a clear epileptic phenotype in DS assembloids. Our human DS cortical assembloids could be pivotal to better understand disease pathogenesis in a human context and to improve preclinical testing of novel advanced therapies.

NOTES

Sleep and temperature dysregulation in a Dravet Syndrome mouse model

Fadila S.[1,2], Beucher B.[3], González-Dopeso Reyes I.[3], Kremer EJ.[3], Rubinstein M.[1,2,4]

[1]Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University.
[2]Goldschleger Eye Research Institute, Sackler Faculty of Medicine, Tel Aviv University.
[3]Institut de Génétique Moléculaire de Montpellier, Université de Montpellier, CNRS, Montpellier.
[4]Sagol School of Neuroscience, Tel Aviv University.

ORAL AND POSTER PRESENTATION

Abstract text: Dravet syndrome (Dravet) is a devastating developmental and epileptic encephalopathy with childhood onset. Most cases of Dravet are caused by loss of function mutations in the SCN1A. Sleep disturbances are very common in Dravet and usually occur because of seizures. Dravet patients often have trouble initiating sleep with difficulties in sleep-wake transitions. Moreover, temperature deficits are prevalent, with reduced sweating and intolerance to cold. Sleep quality is associated with a reduction in body temperature and is believed to be important for sleep homeostasis.

The ventrolateral preoptic area (VLPO) is a sleep-promoting region that is also involved in regulating body temperature. Here, we characterised sleep and thermal dysregulation in a Dravet syndrome mouse model (DS mice). Our measurements revealed a decreased baseline temperature in DS mice and an inability to maintain body temperature in ambient temperatures. Furthermore, ECoG recordings concomitant with body core temperature measurements revealed a failure to reduce body temperature during non-REM sleep (NREM) in DS mice. Importantly, chemogenetic activation of the VLPO ameliorated sleep-promoting deficits and thermal dysregulation in DS mice. Together, our data show a link between sleep and thermal comorbidities in Dravet and demonstrate that alterations in neuronal function in sleep-promoting and thermoregulatory brain regions are involved.

NOTES

Local reactivation of Scn1a gene in a reversible mouse model of Dravet Syndrome

Martina Mainardi[1], Alessia Salamone[1], Claudia Di Berardino[1], Vania Broccoli[1,2], Gaia Colasante[1]

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[2]National Research Council (CNR), Institute of Neuroscience, 20129 Milan, Italy.

ORAL AND POSTER PRESENTATION

Abstract text: Haploinsufficient mutations in SCN1A gene are in 80% of patients the genetic cause of Dravet Syndrome (DS). The characterization of several mouse models of DS provided knowledge on the disease mechanisms.

We recently generated a reversible mouse model of DS (Scn1aStop/+) and proved that Scn1a gene reinstatement also after symptom onset (P30 mice) is sufficient to rescue SUDEP, epileptic phenotype and behavioural alterations (Valassina et al., 2022). Scn1a gene reactivation was achieved by systemic delivery of PHP.eB Adeno-associated virus (AAV) expressing ubiquitous Cre recombinase.

To gain information concerning the role of different anatomical brain regions in DS and the areas that should be prioritised in gene therapy treatments, we exploited the Scn1aStop/+mice to spatially modulate Scn1a reactivation, selecting the hippocampus as first target. Scn1aStop/+ mice were bilaterally injected in the hippocampus with either the PHP.eB-Cre or PHP.eB-Ctrl at post-natal day 30 (P30) followed by implantation with wireless transmitters for video-EEG recording and thermal induction protocol. The two cohorts of animals were comparable in terms of spontaneous seizures and survival while Cre-injected Scn1aStop/+ mice displayed an amelioration of febrile seizures. These data are relevant for the development of more targeted therapies and provide indications on the minimum brain region to be corrected to achieve significant symptomatic amelioration.

NOTES

POSTER PRESENTATIONS ABSTRACTS

(in alphabetical order)

Impact of epilepsy and role of serotonin on ventilatory dysfunctions in a Dravet Syndrome model

Fabrice Duprat[2], Tiffany Migevent[2], Hayet Kouchi[1], Laurent Bezin[1], Luc Zimmer[1], Sylvain Rheims[1], Massimo Mantegazza[2]

[1]Lyon's Neuroscience Research Centre, Lyon, France.
[2]Institute of Molecular and Cellular Pharmacology (IPMC), University Côte d'Azur, CNRS, INSERM, Valbonne, France.

Abstract Text: Sudden and unexpected death in epilepsy (SUDEP) represents a major cause of death in Dravet Syndrome (DS). The main clinical risk factor of SUDEP is the frequency of convulsive seizures. Experimental and clinical data suggest that most SUDEP cases result from postictal brainstem dysfunction, including central respiratory arrest. In Scn1aR1407X/+ mice, a DS mouse model, SUDEP resulted from postictal central apnoea, which subsequently caused bradycardia. This brainstem dysfunction might be favoured by peri-ictal cortical spreading depression (CSD), a self-propagating depolarizing wave that silences neuronal networks. There is evidence suggesting involvement of serotonin (5HT) dysfunction both in the pathogenesis of epilepsy in DS and in seizure-related respiratory dysfunction. In a mouse model of DS, 5HT abnormalities, especially of 5HT1A receptors, have been reported before and after seizure onset.

SUDEP in DS might therefore be the result of a seizure-induced fatal apnoea in a patient who has developed epilepsy-related vulnerability to central respiratory dysfunction favoured by 5HT dysfunction. However, several issues remain to be addressed:

- What is the temporal dynamic of the onset and evolution of the respiratory vulnerability?
- What is the relation between the alterations of the 5HT pathway and epilepsy-related respiratory dysfunction?
- Does modulation of 5HT neuronal activity reduce the risk of epilepsy-related respiratory dysfunction and possibly the risk of SUDEP?

This will be addressed in our project 'SeroDRAVET', funded by the French National Research Agency.

NOTES

Role of arousal mechanisms in Sudden Unexpected Death in Epilepsy (SUDEP) in Scn1a+/- mice

Cyril Lhopitallier[1,2], Tiffany Migevent[1,2], Fabrice Duprat[1,2,3], Massimo Mantegazza[1,2,3] (and the NEUROSENSE consortium)

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Abstract Text: Sudden Unexpected Death in Epilepsy (SUDEP) is a challenge for epileptic patients in general and for Dravet syndrome in particular. There are no methods for predicting and preventing SUDEP. Within the European project Neurosense (NEUROendocrine SENSor for SUDEP prediction and prevention; https://neurosense-project.eu/project/), we have the goal to develop the first SUDEP Medical Device (SMD) prototype to anticipate life-threatening seizures and trigger automatic emergency drug administration to prevent SUDEP.

The basic hypothesis of the project is that dysfunctions in arousal mechanisms are involved in SUDEP. We are developing experimental approaches for chronic quantification of arousal mediators in the Scn1a+/- Dravet syndrome mouse model and correlate their dysfunctions to SUDEP occurrence in mice. These include the establishment of chronic microdialysis methods for quantifying in real time kinetics of neurohormons in parallel with methods of seizure detection. These data will be used to generate a predictive algorithm for SUDEP prediction, which will provide the basis for applying the method to patients. Further experiments will shed more light on the detailed molecular/cellular mechanisms that link these dysfunctions to SUDEP, including effects on cardiorespiratory functions and on brainstem centres involved in cardiorespiratory regulation, which may provide target for developing preventive treatments.

NOTES

Scn1a haploinsufficiency alters postnatal maturation of excitatory cells and synapses in CA1

Steffan P Jones[1], Nathanael O'Neill[1], Sharon Muggeo[2], Gaia Colosante[2], Dimitri M. Kullmann[1], Gabriele Lignani[1]

[1]UCL Institute of Neurology, London.
[2]San Raffaele Scientific Institute, Milano.

Abstract text: Recent studies in mouse models suggest that an "interneuronopathy" alone does not completely explain the cellular and network impairments seen in Dravet Syndrome (DS). Here, we investigate the development of the intrinsic, synaptic, and network properties of CA1 pyramidal cells in a DS model prior to the appearance of overt seizures and prior to the emergence of experimentally detectable disruption to excitation-inhibition balance. We report that the maturation of intrinsic electrophysiological properties of CA1 pyramidal cells is altered by loss of Scn1a and propose that this is explained by reduced intrinsic excitability in early postnatal life, during which Scn1a is normally expressed in hippocampal pyramidal cells alongside the later emergence of defective inhibitory transmission. We also employ a novel ex vivo model of homeostatic plasticity to show altered intrinsic homeostatic responses to induced circuit hyperactivity in pyramidal cells during DS Epileptogenesis.

This study provides evidence for an important role of disrupted postnatal development of pyramidal cells in the earliest stages of DS epileptogenesis and prior to the accepted onset of interneuron dysfunction, suggesting that some outstanding questions in DS pathophysiology may be understood by further exploration of how Scn1a haploinsufficiency affects excitatory transmission.

NOTES

Sigma-1 positive allosteric modulation as a relevant mechanism of action for antiseizure medications

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Abstract text:

Introduction
Fenfluramine is licensed for management of Dravet syndrome. An interaction with Sigma-1 seems to contribute to fenfluramine's effects. Considering its role in homeostasis, modulation of Sigma-1 might also mediate disease-modifying effects. In this first subproject, we addressed the hypothesis that positive allosteric modulation of Sigma-1 exerts antiseizure effects in chronic epilepsy models.

Methodology
A selective positive allosteric Sigma-1 modulator (E1R) and a Sigma-1 antagonist (NE100) were tested in fully kindled mice and an intrahippocampal kainate model (IHK).

Results
In kindled mice, E1R dose-dependently increased seizure thresholds and decreased seizure severity. E1R was well tolerated at all doses. NE100 did not affect thresholds or seizure parameters. However, preexposure to NE100 partly limited E1R's antiseizure effects. In the IHK, E1R exposure did not affect electrographic seizure frequency.

Conclusions
Our findings suggest that positive allosteric modulation of Sigma-1 can affect ictogenesis, spread, and termination of seizure activity. However, the lack of effects in the IHK, argue against a broad-spectrum activity. In follow-up studies, we will assess the antiseizure and disease-modifying effects of E1R in a Dravet mouse model and determine the relative contribution of Sigma-1 interaction to fenfluramine's effects.

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NOTES


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