UNIVERSIDADE FEDERAL DE ALAGOAS
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BRUNA PRISCILA DOS SANTOS

Manipulação funcional de microRNAs na epilepsia do lobo temporal induzida por *Status Epilepticus*

Functional Manipulation of microRNAs in Status Epilepticus-induced Temporal Lobe Epilepsy

Maceió
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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Alagoas para obtenção do título de Doutora em Ciências da Saúde.

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Modulação funcional de microRNAs na Epilepsia do Lobo Temporal induzida por Status Epilepticus/ *Functional Modulation of microRNAs in Status Epilepticus-induced Temporal Lobe Epilepsy*

Tese submetida ao corpo docente do Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Alagoas e aprovada em 28 de novembro de 2020.

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DEDICATÓRIA

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RESUMO

Numerosas evidências têm mostrado que a epileptogênese induzida por *Status Epilepticus* (SE) é acompanhada por um remapeamento de miRNAomas, encorajando uma carga de estudos funcionais para entender o papel e o potencial clínico dessas moléculas na aquisição e manutenção de um estado propenso a epilepsia. Aqui, realizamos uma revisão sistemática para avaliar os estudos de interferência funcional de microRNAs (miRs) na epileptogênese induzida por SE. Selecionamos 4732 citações exclusivas obtidas de vários bancos de dados e do EpimiRBase, até julho de 2020. A extração dos dados incluiu informações sobre a atividade convulsiva, processo neurobiológico, funções cognitivas e do humor. Sessenta e um estudos preencheram os critérios de elegibilidade, fornecendo dados relativos a 36 miRs, dos quais 15 foram investigados independentemente em pelo menos dois estudos. A modulação funcional induziu: i. ação anticonvulsivante no SE (20 miRs) ou convulsão recorrente espontânea (CRE) (17 miRs); ii. efeitos neuroprotetores (25 miRs); iii. resposta anti-inflamatória (7 miRs); iv. diminuição da gliose celular (5 miRs); v. uma redução nas alterações axonais e dendríticas (3 miRs) e vi. melhora na aprendizagem e memória (6 miRs). O único estudo que usou uma abordagem multiplex de antagomir visando os miR-10a-5p, miR-21a-5p e miR-142a-5p mostrou também redução da gravidade do SE, redução da gravidade e ocorrência de CRE. Discutimos o potencial antiepiléptico e de modificação da doença desses achados considerando a consistência dos dados em estudos independentes, os efeitos complementares da modulação bidirecional e o desenho experimental. Dessa forma, a observação crítica destes dados, revelaram lacunas no conhecimento sobre os efeitos da modulação de miRNAs na epileptogênese induzida por SE em modelos experimentais de Epilepsia Lobo Temporal (ELT). A síntese destas informações, portanto, permite uma visão panorâmica da etapa de investigação desses miRNAs e sugere os possíveis passos para os novos estudos abordarem antes da aplicação clínica como alvos terapêuticos.

Palavras-chave: MicroRNA. *Status Epilepticus*. Epileptogênese. Epilepsia do Lobo Temporal. Estudos de Interferência Funcional.

ABSTRACT

Numerous evidences have shown that the SE-induced epileptogenesis is accompanied by a miRNAome remapping, encouraging a burst of functional studies to understand the role and the clinical potential of these molecules on the acquisition and maintenance of an epileptic-prone state. Here, we performed a systematic review to assess the functional interference studies of miRNAs on SE-induced epileptogenesis. We screened 4732 unique citations from several library databases or EpimiRBase up to July 2020. The outcome measures included information on seizure activity, neurobiological process, cognitive and mood functions. Sixty-one studies met eligibility criteria, providing data regarding 36 miRs, of which 15 were investigated independently in at least two studies. The functional modulation elicited: i. anticonvulsant action on SE (20 miRs) or spontaneous recurrent seizure (17 miRs); ii. neuroprotective effects (25 miRs); iii. anti-inflammatory response (7 miRs); iv. cell gliosis decrease (5 miRs); v. a reduction in axonal and dendritic alterations (3 miRs) and vi. learning and memory improvement (6 miRs). The sole study that used an antagomir multiplex approach targeting miR-10a-5p, miR-21a-5p, and miR-142a-5p showed reduced severity of SE as well, reduced severity and occurrence of SRS. We discussed the anti-epileptic and disease-modification potential of these findings considering the data consistency on independent studies, the complementary effects of bi-direction modulation and the experimental design. Thus, the critical observation of these data, revealed gaps in knowledge about the effects of miRNA modulation on SE-induced epileptogenesis in experimental models of Temporal Lobe Epilepsy (TLE). The synthesis of this information, therefore, allows a panoramic view of the stage of investigation of these miRNAs and necessary steps are possible for the new studies to address before clinical application as therapeutic targets.

Keywords: MicroRNA. Status Epilepticus. Epileptogenesis. Temporal Lobe Epilepsy. Functional Interference Study.

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LISTA DE ABREVIATURAS E SIGLAS

ALS: *Amyotrophic Lateral Sclerosis*

ATP: adenosina trifosfato

CAMARADES: *Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies*

COX: *cyclooxygenase*

CRE: Crises Recorrentes e Espontâneas

GFAP: *Glial fibrillary acidic protein*

DG: *dentate gyrus*

EEG: eletroencefalograma/ *electroencephalogram*

ELT: Epilepsia do Lobo Temporal

ELA: Esclerose Lateral Amiotrófica

ELTM: Epilepsia do Lobo Temporal Mesial

HMGB1: High Mobility Group Box 1

IAKA: *intra-amygdala kainic acid*

IL-1β: interleucina 1 beta

IL-6: interleucina-6

IRAK1: *Interleukin 1 Receptor Associated Kinase 1*

LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde

MAGL: mo*noacylglycerol lipase*

MFS: *Mossy Fiber Sprouting*

miR: microRNA

miRNA: microRNA

NF-κB: *nuclear factor kappa B*

PG-E2: *2-prostaglandin*

PILO: Pilocarpina/*Pilocarpine*

PRISMA: *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

RNA: *Ribonucleic acid*

RNA-seq: *RNA-sequencing*

RISC: RNA-induced silencing complex

RT-qPCR: *Quantitative Reverse Transcription PCR*

SE: *Status Epilepticus*

SIGLE: *System for Information on Grey Literature in Europe*

SRS: *Spontaneous Recurrent Seizures*

TLE: *Temporal Lobe Epilepsy*

TNF: Tumor Necrosis Factor

TNF-α: *Tumor Necrosis Factor alpha*

TGF-β: Transforming Growth Factor Beta

TRAF6: *TNF Receptor Associated Factor 6*

TLR4: *Toll-like receptor 4*

UTR: *untranslated region*

SUMÁRIO

1. INTRODUÇÃO

microRNAs (miRNAs) são uma família de pequenos RNAs não codificantes que possuem um papel central na regulação de vários processos fisiológicos (Achkar et al., 2016; Bartel, 2004; Vishnoi & Rani, 2017). Alterações nos miRNAs devido a eventos genômicos ou epigenéticos contribuem para diversas doenças (Ha & Narry Kim, 2014; Rupaimoole & Slack, 2017). Atualmente, existe um inventário de miRNAs cuja alteração no perfil de expressão é conhecida em praticamente todas as condições patológicas, o que revelou vias moleculares associadas à patogênese, bem como biomarcadores para diagnóstico e prognóstico clínico (Condrat et al., 2020; Gareev et al., 2020).

Estudos baseados em modulação funcional de miRNAs através da estimulação ou supressão de seus efeitos confirmaram que a desregulação do miRNA é um mecanismo causal e consequência em muitas doenças, levando a descoberta de potenciais alvos terapêuticos (Esteller, 2011; Monga & Kumar, 2019). O desafio, portanto, é desenvolver estratégias sobre como analisar todas as informações e aplicar às necessidades clínicas. Neste sentido, diversos medicamentos baseados em miRNA já estão em ensaios clínicos de fase I, II e III para várias doenças, mas nenhum deles visa doenças neurológicas e neurodegenerativas (Bajan & Hutvagner, 2020; Rupaimoole & Slack, 2017). Embora, recentemente, o medicamento MRG-107 direcionado ao miR-155 teve sucesso no ensaio pré-clínico para Esclerose Lateral Amiotrófica (ELA) e está entrando no ensaio de fase clínica (Chakraborty et al., 2020).

A Epilepsia do Lobo Temporal Mesial (ELTM) é uma desordem neurológica que representa um dos subtipos de epilepsia mais comuns e clinicamente intratáveis (Alexander et al., 2016; Devinsky et al., 2018; Engel , 1996; Lévesque et al., 2018). A etiopatogenia da ELTM depende de um insulto epileptogênico, como SE, que desencadeia vários processos neurobiológicos que culminam nas Crises Recorrentes e Espontâneas (CREs), características do cérebro epiléptico. Neste sentido, inibir as mudanças prejudiciais iniciais induzidas por SE

pode ser capaz de prevenir a CRE e comorbidades (Boison & Rho, 2020; Löscher, 2020; Łukawski et al., 2018; Miziak et al., 2020; Paudel et al., 2018; Younus e Reddy, 2017).

Atualmente, nenhuma droga usada para combater a epilepsia tem outros efeitos além da diminuição das crises e ainda assim, falham em aproximadamente 40% dos pacientes com ELTM (Klein & Tyrlikova, 2020; Palleria et al., 2015). Por isso, novas terapias têm sido investigadas para atender aos pacientes farmacorresistentes, como por exemplo, estudos que avaliam a modulação funcional de miRNAs usando abordagens farmacológicas e que revelaram efeitos antiepileptogênicos e/ou anticonvulsivantes.

O número considerável de estudos pré-clínicos envolvendo a modulação funcional de miRNA na epileptogênese induzida por SE possibilita a análise abrangente sobre os efeitos complementares e antagônicos da modulação de miRNA no processo epileptogênico. No entanto, identificar os melhores miRNAs como alvo para uma terapêutica eficaz e segura contra uma condição neuropatológica complexa como a ELTM, tem sido um desafio. Portanto, para contribuir sobre o conhecimento de possíveis miRNAs como alvo terapêutico, realizamos uma revisão sistemática com o objetivo de resumir os estudos funcionais existentes que examinam o papel dos miRNAs na epileptogênese induzida por SE e no desenvolvimento de ELT, buscando discutir o potencial clínico desses achados considerando a consistência dos dados em estudos independentes, os efeitos complementares da modulação bidirecional e o desenho experimental utilizado.

A tese está apresentada em formato de artigo, que relata e discute os resultados apresentados pelo desenvolvimento de uma revisão sistemática realizada como trabalho para conclusão do doutorado.

2. ARTIGO - *Functional Modulation of microRNAs in Status Epilepticus-induced Temporal Lobe Epilepsy*

Abstract

Numerous evidences have shown that the SE-induced epileptogenesis is accompanied by a miRNAome remapping, encouraging a burden of functional studies to understand the role and the clinical potential of these molecules on the acquisition and maintenance of an epileptic-prone state. Here, we performed a systematic review to assess the functional interference studies of miRNAs on SE-induced epileptogenesis. We screened 4732 unique citations from several library databases or EpimiRBase up to July 2020. The outcome measures included information on seizure activity, neurobiological process, cognitive and mood functions. Sixty-one studies met eligibility criteria, providing data regarding 36 miRs, of which 15 were investigated independently in at least two studies. The functional modulation elicited: i. anticonvulsant action on SE (20 miRs) or spontaneous recurrent seizure (17 miRs); ii. neuroprotective effects (25 miRs); iii. anti-inflammatory response (7 miRs); iv. cell gliosis decrease (5 miRs); v. a reduction in axonal and dendritic alterations (3 miRs) and vi. learning and memory improvement (6 miRs). The sole study that used an antagomir multiplex approach targeting miR-10a-5p, miR-21a-5p, and miR-142a-5p showed reduced severity of SE as well, reduced severity and occurrence of SRS. We discussed the anti-epileptic and disease-modification potential of these findings taking into account the data consistency on independent studies, the complementary effects of bi-direction modulation and the experimental design. Thus, the critical observation of these data, revealed gaps in knowledge about the effects of miRNA modulation on SE-induced epileptogenesis in experimental models of Temporal Lobe Epilepsy (TLE). The synthesis of this information, therefore, allows a panoramic view of the stage of investigation of these miRNAs and necessary steps are possible for the new studies to address before clinical application as therapeutic targets.

Introduction

microRNAs (miRNAs) are a family of small (18-22 base pair) endogenous non-coding RNAs that play a central role in the regulation of numerous physiological processes (LEE; FEINBAUM; AMBROS, 1993). Each miRNA fitted in the multi-enzyme RNA-induced silencing complex (RISC) can anneal on 3′ untranslated region (3′ UTR) of their correspondent mRNA targets to induce degradation or a reduction in the translational efficiency (ACHKAR; CAMBIAGNO; MANAVELLA, 2016; BARTEL, 2004; VISHNOI; RANI, 2017). There is a plethora of evidence that changes in these molecules due to genomic or epigenetic events contribute to many diseases (HA; NARRY KIM, 2014; RUPAIMOOLE; SLACK, 2017). The first big wave of these studies came from large-scale gene expression approaches using microarray hybridization platforms and lately RNA-seq. Currently, there is an inventory of miRNA whose alteration in the expression profile is known in practically all pathological conditions, which has revealed molecular pathways associated with pathogenesis as well as biomarkers for diagnosis and clinical prognosis (CONDRAT et al., 2020; GAREEV et al., 2020). The second wave was based on the functional modulation of miRNA through stimulation or suppression of its effects by using miRNA-enhancing molecules (mimics) or oligonucleotide-based antisense inhibitors (antagomirs). The results confirmed that miRNA dysregulation is a causal mechanism as well as consequence in many diseases leading to the discovery of potential therapeutic targets (ESTELLER, 2011; MONGA; KUMAR, 2019). In the past decade, significant improvements in the chemical and structural designs of mimic and antagomirs as well as in delivery vehicle technology burst the functional studies (Setten et al., 2019; Wang et al., 2019). The running challenge is to develop strategies on how to analyze this immense set of information for clinical needs. Many miRNA-based drugs are in phase I, II and III clinical trials for various diseases, but none of them target neurological and neurodegenerative conditions (BAJAN; HUTVAGNER, 2020; RUPAIMOOLE; SLACK, 2017). Recently, the MRG-107 drug targeting miR-155 succeeded in the pre-clinical trial for

Amyotrophic Lateral Sclerosis (ALS) and is entering clinical phase trial (CHAKRABORTY et al., 2020).

Mesial Temporal Lobe Epilepsy (mTLE) is typified by spontaneous recurrent seizures (SRS) that arise from the limbic system and represents one of the most common and medically intractable epilepsy subtypes (ALEXANDER; MAROSO; SOLTESZ, 2016; DEVINSKY et al., 2018; ENGEL, 1996; LÉVESQUE; RAGSDALE; AVOLI, 2018). The mTLE etiopathogenesis depends on an epileptogenic insult, such as Status Epilepticus (SE), which triggers disturbance in the blood-brain barrier (LÖSCHER; FRIEDMAN, 2020) and enduring changes in the hippocampus, including selective neurodegeneration (CASTRO et al., 2011; MELO et al., 2016), neuroinflammation (RANA; MUSTO, 2018a; VEZZANI; GRANATA, 2005), astrogliosis (EID et al., 2019), microgliosis (HIRAGI; IKEGAYA; KOYAMA, 2018), aberrant neurogenesis (HATTIANGADY; SHETTY, 2008; LONGA et al., 2017) , ectopic cell migrations and morphological and spatial neurites alterations (CAVARSAN et al., 2018; HATTIANGADY; SHETTY, 2010; NIRWAN; VYAS; VOHORA, 2018; PITKÄNEN et al., 2015). Stopping the SE-induced early detrimental changes in the hippocampus may be capable of preventing the SRS and comorbidities (BOISON; RHO, 2020; LÖSCHER, 2020; ŁUKAWSKI et al., 2018; MIZIAK et al., 2020; PAUDEL et al., 2018; YOUNUS; REDDY, 2017). Unfortunately, no drug used to combat epilepsy has other effects aside from seizure suppression and yet failing for approximately 40% of mTLE patients (KLEIN; TYRLIKOVA, 2020; PALLERIA et al., 2015).

Over the last decade, numerous evidence has shown that the SE-induced epileptogenesis is accompanied by a miRNAome remapping (BENCUROVA et al., 2017; COSTARD et al., 2019; DE ARAÚJO et al., 2016; GITAÍ et al., 2020; KRETSCHMANN et al., 2014; RAOOF et al., 2017, 2018; SIMONATO, 2018; TANG et al., 2019; YAN et al., 2017). Differential miRNA profiles have been assigned to several post-SE models and compared with each other (KOROTKOV et al., 2017). EpimiRBase is an up-to database containing all publications of

miRNA and epilepsy in experimental models and humans, including the in-vivo functional reports (MOONEY et al., 2016). The functional modulation of a set of these miRNAs by using pharmacological (mimic/antagomir) or genetic approaches has revealed anticonvulsant and/or antiepileptogenic effects, though no miRNA-based therapy has been reached clinical trials in epilepsy (RUPAIMOOLE; SLACK, 2017; STEIN; CASTANOTTO, 2017; TIWARI; PEARISO; GROSS, 2018). The major obstacle is to identify the best miRNAs as the target of an efficacious and safe therapeutic against a complex neuropathological condition such as mTLE. Moreover, the multi-targeting actions of miRNAs are hard to tune and can lead to several undesirable effects (BAJAN; HUTVAGNER, 2020).

On the other hand, the availability of a considerable number of preclinical studies involving functional modulation of miRNA on SE-induced epileptogenesis allows a comprehensive analysis by carefully assessing the complementary and antagonistic effects of miRNA modulation on the epileptogenic process. Certainly, the accumulated knowledge will lead to a better understanding of the evolution of SE into chronic TLE and consequently will enable miRNAs-based therapeutics to move to clinical trials combating the mTLE. The aims of this systematic review, therefore, were to summarize existing functional studies examining the role of miRNAs on SE-induced epileptogenesis and development of TLE. Moreover, we discuss the clinical potential of these findings considering the data consistency on independent studies, the complementary effects of bi-direction modulation and the experimental design.

Methodology

The systematic review was conducted and reported in accordance with the PRISMA guidelines (MOHER et al., 2016) and the protocol was registered on the international prospective register of systematic reviews (PROSPERO registration number: CRD42019141099. Available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=141099.

Search strategy

We performed a systematic literature search of PubMed, Embase, Scopus, LILACS, Google Scholar, SIGLE (System for Information on Grey Literature in Europe) up to July 2020 and EpimiRBase up to October 2019 using the following combinations of relevant keywords: “gene expression” AND “temporal lobe epilepsy”, “up-regulation” OR “down regulation” AND “temporal lobe epilepsy”, “epigenetic” AND “temporal lobe epilepsy”, “RNA interference” OR “RNAi” OR “gene silencing” AND “temporal lobe epilepsy”, “Biomarker” AND “temporal lobe epilepsy”, "non-coding RNA" AND "temporal lobe epilepsy", "gene regulation" AND "temporal lobe epilepsy", "gene knockdown" AND "temporal lobe epilepsy".

Selection criteria

We included studies investigating functional interference on SE-induction epileptogenesis. The eligibility criteria were i. original research, ii. Studies based on SE-induced models, iii. Studies based on functional modulation of miRs. Selected articles were filtered according to these criteria in three steps (see **Fig 1**): e i. duplicated publications from the database were excluded; ii. non-relevant studies were excluded, such as human studies, *in vitro* studies, *in silico* studies, case reports, reviews, book chapters, thesis, congress, symposium, colloquium, meeting, posters; iii. relevant studies were screened to exclude those conducting experimental analysis without functional modulation of miRs in SE-induced models. Titles and/or abstracts retrieved using the search strategy were screened independently by two review authors (Erivaldo Júnior and Pedro Tibúrcio) to identify studies that potentially matched the eligibility criteria (step 1 and 2). The full text of these potentially eligible studies was retrieved and independently assessed for eligibility by two review team members (Bruna Santos and Mykaella Araújo). Any disagreement between them over the eligibility of studies were resolved through discussion with a third reviewer (Daniel Gitaí).

Data extraction

Data extracted included information on: i. miRNA identification; ii. functional interference approaches and methodologies; iii. neurobiological process assessed (neuroinflammation, neurodegeneration, neurogenesis, gliosis (microgliosis and astrogliosis), axonal and dendritic plasticity (axonal damage, dendritic plasticity, and mossy fiber sprouting (MFS)), altered gene expression); iv. Cognitive and mood functions (memory impairment, depression-like) e v. SRS and SE (seizures frequency, score, duration, and quantitative evaluation of EEG).

Quality assessment

The methodological quality of included studies was assessed independently by two investigators using criteria from the CAMARADES checklist (MACLEOD et al., 2004) adapted to epilepsy animal models (SIMONATO et al., 2017): i. Publication in a peer-reviewed journal, ii. Random allocation to group, iii. Blinded conduct of the experiment, iv. Blinded assessment of outcome, v. Sample size calculation, vi. Reporting of animals excluded from analysis and reasons for exclusion (e.g., health status, general conditions, or other parameters), vii. Reported health status and general condition, viii Monitoring duration longer than 1 week (for adult animal models), ix. Continuous (vs. discontinuous) monitoring (for adult animal models), x. Video-EEG monitoring, xi. Information about the course of spontaneous recurrent seizures (i.e., progression/regression/remission). Each study was given a quality score out of a possible total of 11 points, and the group median was calculated. Disagreements were resolved by consensus. Due to high heterogeneity in study design and outcome measurements among the included articles, a meta-analysis was not performed. Instead, we conducted a narrative synthesis of the evidence.

Results

Overview

Our search returned 11317 citations, 6585 of which were duplicated. Of the 4732 unique citations, 3915 were excluded because they were not relevant to the current review. Of 817 relevant studies identified, 61 met the predetermined inclusion criteria, providing data regarding 36 miRs, of which 15 were investigated independently in at least two studies. (**Fig 1, Table 1 and S1 Table).** Eight miRs (146a, 22, 23a, 124, 137, 139-5p, 181b and 219) were modulated in a bi-direction way (inhibition and stimulation), while 27 miRs were modulated by either inhibition (134, 155, 10a-5p, 21a-5p, 27a-3p, 34a, 132, 142a-5p, 181a, 324-5p, 21-5p, 129-5p, 135a, 142-5p, 145, 183, 187, 199a-5p, 200c-3p, 203, 210 and 431-5p) or stimulation (23b-3p, 96, 206, 494 and let-7b), only (**Table 2**). The functional assays were performed modulating the miR expression abundance by mimic/agomir alone (n=9), by antagomir/inhibitor, (n=40) alone, or by both approaches (n= 10); Only 2 studies were based in genetic interference, including knockout and transgenic models **(Table 2)**.

The studies included in the review were conducted in SE-model induced by PILO (n= 30), Kainate (n=29) and electrical stimulation (n=2). Most functional interventions were performed before the SE-induction (n= 25, 41%) or in the early stages (first week) of epileptogenesis (n=27, 44%), and only 4 interventions carried out the intervention after SRS onset (chronic phase). The vast major of studies evaluated the effect on behavioral or EEG seizures either during SE (n=27) or during spontaneous and recurrent seizures (n= 22) **(Table 3)**. The main neurobiological processes assessed were neuroinflammation, neurodegeneration, reactive gliosis and neural plasticity. Only 1 study evaluated aberrant neurogenesis. Regarding executive functions, 10 studies evaluated memory and cognitive performances **(Table 2, 4 and S2 Table)**.

Effects on behavioral and EEG Seizures

We analyzed data regarding the frequency, duration, and severity of behavioral and EEG seizures. An anticonvulsant action on SE was observed by the inhibition of miRs 146a, 134, 155, 10a-5p, 21a-5p, 132, 142a-5p, 324-5p, 21-5p, 129-5p, 142-5p, 183, 199a-5p, 431-5p

and 200c-3p or by the stimulation of miRs 146a, 23b-3p, 181b, 206, 219 and 494. Regarding chronic phase, the attenuation of SRS was observed by the inhibition of miRs 132, 134, 155, 10a-5p, 21a-5p, 23a, 142a-5p, 324-5p, 135a, 203, 21-5p and 27a-3p or by the stimulation of miRs 22, 146a, 124, let-7b and 137. However, only 3 miRs (146a, 324-5p and 203) of them were manipulated after the animal became epileptic. None of the modulations reached full control of the seizures. Most of miRs submitted to a bi-direction modulation showed complementary effects (146a, 22, 124, 137, and 219). Conversely, the miR-211 elicited only proconvulsant effects on both SE and SRS **(Tables 2 and 4**).

Effects on Neurobiological Process

The neurobiological processes were assessed by histochemistry staining or biomarkers quantification based on immunohistochemistry, RT-qPCR, Western blotting, and Elisa (**S2 Table**). In the chronic phase, the studies (4) were restricted to evaluating neuroinflammation and neurodegeneration (**Table 3 and S2 Table**).

The neuronal damage and cell death were ameliorated by stimulation of miRs 96, 146a, 181b, 206 and 494 and by inhibition of miRs 146a, 134, 155, 10a-5p, 21a-5p, 27a-3p, 34a, 132, 142a-5p, 181a, 324-5p, 21-5p, 129-5p, 142-5p, 145, 183, 199a-5p, 431-5p, 23a, 200c-3p and 210 (**Table 4**). These neuroprotective effects were reported for hippocampus and other brain structures.

The quantification of inflammatory cytokines revealed that 7 miRs attenuated the inflammatory response as a consequence of the functional inhibition (146a, 155, 27a-3p, 200c-3p and 181a-5p) or stimulation (146a, let-7b and 206).

Regarding reactive gliosis, the inhibition of miRs 22, 181a-5p and the stimulation of let-7b decreased the microgliosis; while the functional interference of miRs 134, 181a-5p, 200c-3p and let-7b reduced the astrogliosis as assessed by GFAP detection. Most of these miRs showed complementary effects when submitted to a bi-direction modulation. Conversely, four

miRs showed only enhancer effects on proinflammatory cytokines levels (miR187, 22 and 124), microgliosis (124) and astrogliosis (none).

The neural plasticity was assessed by axonal and dendritic alteration. The inhibition of miRs 132, 134 and 181a-5p reduced the aberrant mossy fiber, dendrite spine density and aberrant formation of dendritic spines. Conversely, inhibition of miR-22 increased the dendritic diameter and mossy fibers (**Table 4 and S2 table)**. The only study assessing the neurogenesis showed that inhibition of miR-22 enhanced genesis of new neurons on the hippocampus, including within the undamaged contralateral dentate gyrus (DG). The newly formed neurons underwent aberrant migration within the granule cell layer or into ectopic sites (BEAMER et al., 2018).

Effects on Cognitive functions

Cognitive functions were investigated by mostly Morris Water Maze and Object Location Test at some weeks after SE termination. An improvement of the learning and memory abilities was observed by the stimulation of miR-181b; and by the inhibition of miRs 134, 23a, 181a-5p, 21-5p and 145. Conversely, the functional interference in miR-22 and miR-23a results in the increase of anxiety and of cognitive impairment, respectively.

Discussion

In this review, we assessed 61 eligible studies to provide an updated perspective on the accumulating evidence on functional modulation of 36 miRs on SE-induced epileptogenesis. In general, the miRs showed effects on SE and its neurobiological consequences as well as SRS. Fifteen miRs were investigated independently in at least two studies and only 3 (miRs 146a, 155 and 134) miRs showed some incoherent results for the modulations in the same direction.

MiR-146a is highly expressed in neuron and astrocytes during epileptogenesis (Aronica et al., 2010; Iyer et al., 2012; Kong et al., 2015; Koturbash et al., 2011; Li et al., 2010). Only

the miR-146 presented an inconsistent seizure-suppressing effect. Additionally, He et al showed that down-regulating miR-146a by intracerebroventricular injection of antagomir decreased the frequency and duration of seizures during the electrical-induced SE (HE et al., 2016a) On the other hand, in a kainic model, Iori et al showed that the knock-down of miR-146a by i.c.v. administration of antagomiR mediated a significant increase in seizure number/duration and decreased the latency to seizure onset. Similarly, two studies showed that the inhibition of miR-155 ameliorates the SE while one study in PILO-induced SE revealed no seizure-suppressing action on SE (CAI et al., 2016; FU et al., 2019; HUANG; ZOU; LU, 2018). These apparent contradictions could be ascribed to the different experimental designs.

The SE triggers a plethora of epigenetic-dependent enduring changes in the hippocampus and brain structures, leading to cognitive impairment and increased risk of TLE (YOUNUS; REDDY, 2017). Epileptogenesis refers to the conversion of the normal brain into one capable of generating spontaneous seizure activity and can sustain even after the onset of SRS which makes this process progressive (DINGLEDINE; VARVEL; DUDEK, 2014). Taking account, the consistent data based on independent studies or on complementary effects of bi-direction modulation of miR expression, we observed 11 miRs (146a, 134, 132, 10a-5p, 21a-5p, 23a, 27a-3p, 34a, 142a-5p, 137 and 181a-5p) with a regulatory role in neurodegeneration, neuroinflammation, gliosis, axonal and dendritic plasticity, cognitive functions and seizures.

Neurodegeneration has been proposed to be an integral part of SE-induced epileptogenesis (DINGLEDINE; VARVEL; DUDEK, 2014). SE causes substantial brain damage in glutamatergic principal neurons and inhibitory interneurons of vulnerable areas in limbic structures, such as the hippocampus (KURUBA et al., 2011; SHETTY; HATTIANGADY; RAO, 2009). The cell-death can be mediated by non-inflammatory (e.g. apoptosis) or inflammatory (e.g. necrosis) processes (DINGLEDINE; VARVEL; DUDEK, 2014). Mir-134 is a neuron-specific miRNA that regulates hippocampal function (e.g. memory)

and homeostasis (MORRIS; RESCHKE; HENSHALL, 2019). We found five independent studies showing that animals injected with antagomir against miR-134 had a strong reduction of SE-induced neuronal death at earlier epileptogenesis or chronic phase. Similarly, antagomir treatment for miR-181a, miR-27a-3p and miR132 lead a consistent decrease in neurodegeneration based on independent studies (HUANG et al., 2014; JIMENEZ-MATEOS et al., 2011; LU et al., 2019; REN; ZHU; LI, 2016; YUAN et al., 2016). The neuroprotective effects may be achieved by various mechanisms, including apoptotic pathways.

SE induces a cascade of persistent inflammatory state in the microenvironment of neural tissue (WANG; CHEN, 2018). The fast response is characterized by an increase of pro-inflammatory molecules released from activated glial cells, neurons and blood-brain barrier (BBB) (CHENG et al., 2018; GIANNONI et al., 2018; KLEMENT et al., 2019; MARCHI; LERNER-NATOLI, 2013; VAN VLIET et al., 2018). The inflammatory molecules trigger associated pathways in the target cells, contributing to BBB disruption, cell infiltrating into the brain and to increase the cytokine level in the epileptogenic brain tissue. The most studied inflammatory mediators and pathways on epileptogenesis are Interleukin(IL)-1β, Tumor Necrosis Factor (TNF), Transforming Growth Factor (TGF)-β, High Mobility Group Box 1 (HMGB1), ATP, monoacylglycerol lipase (MAGL), and cyclooxygenase (COX)-2-prostaglandin (PG) E2 axis (VAN VLIET et al., 2018; VEZZANI; BALOSSO; RAVIZZA, 2019). The neuroinflammatory response may sustain neuronal damage and contribute to the development of epilepsy (JANIGRO, 2012). Mir-146 was consistently observed as a regulator of inflammatory responses over epileptogenesis. The studies showed that the inhibition of miR-146 plays a role in attenuating SE-induced inflammatory response, and this effect is reversed in functional stimulation tests (HE et al., 2016b; IORI et al., 2017; LI et al., 2018a; ZHANG et al., 2018). Evidences on SE evoked by electrical stimulation or by chemoconvulsives pointed that suppression of miR-146 reduced the pro-inflammatory molecules levels, such as TNF-α, IL-1β and IL-6, NF-*κ*B, IRAK1, TRAF6 and TLR4. The modulation of miR-155 has also been

characterized as a negative regulator of SE-induced neuroinflammation. Two independent studies showed that the inhibition of miR-155 at earlier stages of epileptogenesis counteracted the inflammatory process by reducing pro-inflammatory cytokines expression, such as TNF-α (FU et al., 2019; LI et al., 2018b).

The BBB disruption is a relevant factor in astrocyte and microglia activation (OBY; JANIGRO, 2006; SHIGEMOTO-MOGAMI; HOSHIKAWA; SATO, 2018). Gliosis is one of well documented pathological features of SE-induced epileptogenesis and it is associated with the release of pro-inflammatory mediators (RANA; MUSTO, 2018b; SHARMA; PUTTACHARY; THIPPESWAMY, 2019). We found that modulation of 6 miRs (22, 134, 181a-5p, 200c-3p, 124 and let-7b) has consequences for astrogliosis and microgliosis. However, none of them was tested for reproducibility in independent studies or for complementary effects in bi-directional modulation approaches.

Neural plasticity is a hallmark feature of epilepsy models and in human TLE, reflecting neurites swelling, loss and sprouting (JARERO-BASULTO et al., 2018). These structural changes can contribute to neuronal hyperexcitability and SRS onset (Varma et al., 2019). The miR-132 and miR-134 expressions are induced by epilepsy-inciting events in humans or SE-models (TIWARI; PEARISO; GROSS, 2018). Independent studies showed that the administration i.c.v. of the Antagomir for these miR suppressed the Mossy Fiber Sprouting (MFS) and dendrite spine density in the hippocampus of animals submitted to chemoconvulsants induced SE.

Clinical Relevance

Despite intense research over the last decades uncovering the functional role of miRs in epileptogenesis, no miRNA-based drugs have reached clinical trials in epilepsy. The search for new epilepsy treatments depends on the screening of drugs that control seizures (anticonvulsant action) or that have prophylactic action (antiepileptogenic action) (LÖSCHER, 2020; MIZIAK et al., 2020). In this case, the proposal is to inhibit the effects of SE to block the onset of

spontaneous seizures (prevention therapy); or to lead to less severe form of the disease (disease modification therapy). These interventions must be tested before the onset of spontaneous seizures. Here, the assessment of the clinical potential of miRs was hedged because most studies carried out the functional intervention before the SE induction. In fact, the intervention affects SE limiting its long-term consequences and, therefore, can mistake the effects resulting from "initial insult modification" as "true" antiepileptogenic action (LÖSCHER; BRANDT, 2010).

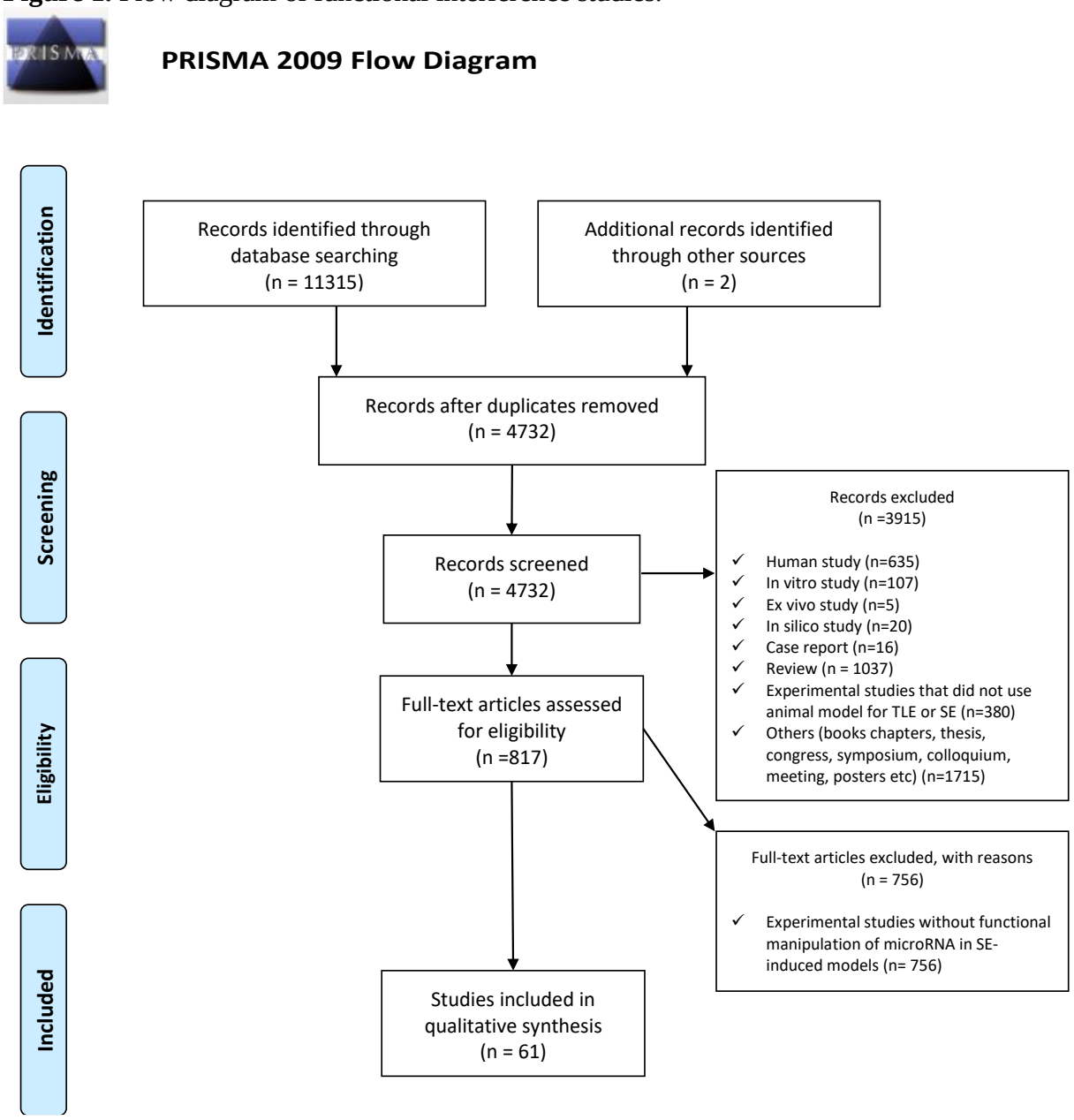
Restricting the analysis to studies in which the functional assay was performed after SE termination, no miR intervention leads to complete prevention of SRS onset. On the other hand, 10 miR (134, 155, 132, 23a, 181b, 135a, 137, 183, 494 and 200c-3p) reduced seizure frequency, duration, or severity. The administration of Antagomir-MiR-134 showed a dramatic SRS-suppressing action during long-term monitoring in different SE-induced epileptogenesis models (GAO et al., 2019; JIMENEZ-MATEOS et al., 2012; RESCHKE et al., 2017, 2019). The anti-seizure mechanism of miR-134 inhibition was associated with the de-repression of Limk1(JIMENEZ-MATEOS et al., 2012). Similarly, treatment with antagomir-132 improved the frequency of SRS as evidenced in two independent studies (Huang et al., 2014; Yuan et al., 2016), however, the underlying mechanism remains to be investigated. Moreover, the miRs 134, 23a and 181b reduced epilepsy-associated comorbidities such as cognitive decline.

An important prerequisite for designating an antiepileptic effect is perform the preclinical tests for anticonvulsant action when the animals have already become epileptic (LÖSCHER, 2020). We observed that only 4 studies met this condition. The inhibition of miR-324-5p and miR-203 showed anti-seizure effects typified by reduction of SRS frequency. The sole study that used an antagomir multiplex approach ("combi-antimiR") targeting miR-10a-5p, miR-21a-5p, and miR-142a-5p showed reduced occurrence and severity of SRS on intra-amygdala kainic acid (IAKA) model (VENØ et al., 2020). Notably, the underlying anti-seizure mechanism depends on the derepression of a common target TGFβRII whose inhibition blocked the antiepileptic action of the combi-antimiR.

Conclusion

The advancement in the understanding of the functions of miRNAs in epilepsy has stimulated in-depth studies of functional modulation, seeking to develop new therapies targeting miRNAs. In this systematic review, we observed gaps in knowledge about the effects of this modulation on SE-induced epileptogenesis in experimental ELT models. The tuning of the results reinforces and extends the evidence that miRNAs are an important class of regulatory element in epilepsy with therapeutic potential for crisis control. In addition, this information allows a panoramic view of the stage of investigation of these miRNAs with therapeutic potential, their limitations, and possible steps for further studies before clinical application. However, the identification of these miRNAs with therapeutic potential can be considered as one of the most significant advances with translational potential for patients with ELTM, and the next generation drugs can be considered for the complete remission of crises.

Figure 1. Flow diagram of functional interference studies.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 1. Functional interference studies with microRNAs.

Nº	non-coding gene	Study
1	microRNA-146a	Zhang et al. (2018)
	microRNA-146a	Li et al. (2018)
	microRNA-146a	Iori et al. (2017)
	microRNA-146a	Zhang et al. (2018)
	microRNA-146a	Huang et al. (2019)
	microRNA-146a	He et al. (2016)
	microRNA-146a	Tao et al. (2017)
	microRNA-146a-5p	Deng et al. (2019)
2	microRNA-134	Reschke et al. (2019)
	microRNA-134	Gao et al. (2019)
	microRNA-134	Rodriguez et al. (2017)
	microRNA-134	Jimenez-Mateos et al. (2014)
	microRNA-134	Sun et al. (2017)
	microRNA-134	Jimenez-Mateos et al. (2012)
	microRNA-134	Reschke et al. (2017)
3	microRNA-155	Cai et al. (2016)
	microRNA-155	Li et al. (2018)
	microRNA-155	Fu et al. (2019)
	microRNA-155-5p	Huang et al. (2018)
4	microRNA-22	Jimenez-Mateos et al. (2015)
	microRNA-22	Engel et al. (2017)
	microRNA-22	Beamer et al. (2018)
	microRNA-22	Silva et al. (2020)
5	microRNA-132	Huang et al. (2014)
	microRNA-132	Jimenez-Mateos et al. (2011)
	microRNA-132	Yuan et al. (2016)
6	microRNA-10a-5p	Veno et al. (2019)
	microRNA-10a-5p	Veno et al. (2020)
7	microRNA-21a-5p	Veno et al. (2019)
	microRNA-21a-5p	Veno et al. (2020)
8	microRNA-23a	Zhu et al. (2019)
	microRNA-23a	Zhu et al. (2019)
9	microRNA-27a-3p	Veno et al. (2019)
	microRNA-27a-3p	Lu et al. (2019)
10	microRNA-34a	Sano et al. (2012)
	microRNA-34a	Hu et al. (2012)
11	microRNA-124	Brennan et al. (2016)
	microRNA-124	Wang et al. (2016)
12	microRNA-142a-5p	Veno et al. (2019)
	microRNA-142a-5p	Veno et al. (2020)
13	microRNA-181a	Ren et al. (2016)

	microRNA-181a-5p	Kong et al. (2020)
14	microRNA-181b	Zhang et al. (2015)
	microRNA-181b	Wang et al. (2019)
15	microRNA-324-5p	Tiware et al. (2019)
	microRNA-324-5p	Gross et al. (2016)
16	microRNA-21-5p	Tang et al. (2018)
17	microRNA-23b-3p	Zhan et al. (2016)
18	microRNA-96	Gan et al. (2017)
19	microRNA-129-5p	Rajman et al. (2017)
20	microRNA-135a	Vangoor et al. (2018)
21	microRNA-137	Wang et al. (2018)
22	microRNA-139-5p	Alsharafi et al. (2016)
23	microRNA-142–5p	Zhang et al. (2020)
24	microRNA-145	Zhao et al. (2019)
25	microRNA-183	Feng et al. (2019)
26	microRNA-187	Alsharafi et al. (2015)
27	microRNA-199a-5p	Wang et al. (2016)
28	microRNA-200c-3p	Du et al. (2019)
29	microRNA-203	Lee et al. (2017)
30	microRNA-206	Wu et al. (2019)
31	microRNA-211	Chen et al. (2016)
32	microRNA-211	Bekenstein et al. (2017)
33	microRNA-219	Zheng et al. (2016)
34	microRNA-431-5p	Veno et al. (2019)
35	microRNA-494	Yinbao et al. (2020)
36	microRNA-Let-7b	Han et al. (2020)

Table 2. Details of the biological processes investigated in the studies of functional interference with microRNAs.

MicroRNA	type of interference	Neuroinflammation	Neurodegenaration	Neurogenesis	Gliosis	axonal and dendritic plasticity	Cognitive function	SE	SRS	Reference
146a	antagomiR	reduction	reduction	no investigated	no investigated	no investigated	no investigated	Reduction[a] increase[b]	no investigated	He et al. (2016)[a], Iori et al. (2017)[b], Li et al. (2018), Zhang et al. (2018)a
	inhibitor	reduction	reduction	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Zhang et al. (2018)b, Huang et al. (2019)
	mimic	reduction	reduction[c] no difference[d]	no investigated	no investigated	no investigated	no investigated	reduction	reduction	Tao et al. (2017)[c], Iori et al. (2017)[d], Deng et al. (2019)
	agomiR	increase	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	increase	Li et al. (2018)
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
134	antagomiR	no investigated	reduction[a,d,f] no difference[e]	no investigated	reduction	reduction	improvement[d] no difference[b]	reduction[b,f] no difference[g]	reduction	Jimenez-Mateos et al. (2012)[a], Jimenez-Mateos et al. (2014)[b], Rodriguez et al. (2017)[c], Sun et al. (2017)[d], Reschke et al. (2017)[e], Gao et al. (2019)[f], Reschke et al. (2019)[g]
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
155	antagomiR	reduction	reduction	no investigated	no investigated	no investigated	no investigated	reduction[c,d] no difference[a]	reduction	Cai et al. (2016)[a], Li et al. (2018)[b], Huang et al. (2018)[c], Fu et al. (2019)[d]
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
22	antagomiR	increase	no investigated	increase	increase (astrogliose)[a] reduction (microgliose)[a]	increase	worsens	no difference	increase	Jimenez-Mateos et al. (2015)[a], Engel et al. (2017)[b], Beamer et al. (2018)[c]
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	Jimenez-Mateos et al. (2015)
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no difference	no investigated	no difference	no investigated	no investigated	no difference	increase	Silva et al., 2020

132	antagomiR	no investigated	reduction	no investigated	no investigated	reduction	no investigated	reduction[a] no difference[b]	reduction	Jimenez-Mateos et al. (2011)[b], Huang et al. (2014)[a], Yuan et al. (2016)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
10a-5p	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	reduction	Veno et al. (2019), Veno et al. (2020)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
21a-5p	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	reduction	Veno et al. (2019), Veno et al. (2020)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
23a	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	improvement	no investigated	reduction	Zhu et al. (2019)a, Zhu et al. (2019)b
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	increased	no investigated	no investigated	no investigated	worsens	no investigated	no investigated	Zhu et al. (2019)a, Zhu et al. (2019)b
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
27a-3p	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Veno et al. (2019)
	inhibitor	reduction	reduction	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	Lu et al. (2019)
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	no difference	no investigated	Sano et al. (2012), Hu et al. (2012)

34a	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
124	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	increase	Wang et al. (2016)
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	Wang et al. (2016)
	agomiR	increased	no investigated	no investigated	increased	no investigated	no investigated	no investigated	no difference	Brennan et al. (2016)
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
142a-5p	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	reduction	Veno et al. (2019), Veno et al. (2020)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
181a	antagomiR	reduction	reduction	no investigated	reduction	reduction	improvement	no investigated	no investigated	Ren et al. (2016), Kong et al., 2020
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
181b	antagomiR	no investigated	increased	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Zhang et al. (2015)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Zhang et al. (2015)
	agomiR	no investigated	reduction	no investigated	no investigated	no investigated	improvement	reduction	no investigated	Wang et al. (2018)
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	reduction	Gross et al. (2016), Tiware et al. (2019)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x

324	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	improvement	reduction	no investigated	Tang et al. (2018)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
21-5p	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
23b-3p	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	no investigated	Zhan et al., 2016
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
96	mimic	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Gan et al. (2017)
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	no investigated	Rajman et al. (2017)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
129-5p	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	Vangoor et al. (2018)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
135a	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x

	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
137	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	increased	Wang et al. (2018)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	Wang et al. (2018)
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
139-5p	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Alsharafi et al. (2016)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Alsharafi et al. (2016)
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
142-5p	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	no investigated	Zhang et al. (2020)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
145	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	improvement	no investigated	no investigated	Zhao et al. (2019)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
183	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	no investigated	Feng et al. (2019)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	antagomiR	increased	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Alsharafi et al. (2015)

187	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
199a-5p	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	no investigated	Wang et al. (2016)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
200c-3p	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	reduction	reduction	no investigated	reduction	no investigated	no investigated	reduction	no investigated	Du et al., (2019)
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
203	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	Lee et al. (2017)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
206	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	reduction	reduction	no investigated	no investigated	no investigated	no investigated	reduction	no investigated	Wu et al. (2019)
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
210	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	Chen et al., 2016
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x

	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
211	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	increased	increased	Bekenstein et al., 2017
219	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	increased	no investigated	Zheng et al. (2016)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	no investigated	Zheng et al. (2016)
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
431-5p	antagomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	reduction	no investigated	Veno et al. (2019)
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
494	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	agomiR	no investigated	reduction	no investigated	no investigated	no investigated	no investigated	no investigated	reduction	Qi et al. (2020)
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
Let-7b	antagomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	inhibitor	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	mimic	reduction	no investigated	no investigated	reduction	no investigated	no investigated	no investigated	reduction	Han et al., 2020
	agomiR	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x
	genetic	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	no investigated	x

Table 3. Details of the functional interference of the microRNAs and epileptogenic effects.

microRNA	model SE induction	Technique used for gene manipulation	Chemical Modification of Oligonucleotides	Dose administration	Route administration	time of interference	Reference
146a	PILO	antagomir	AntagomiR-146a (5'-ASASCCCAUGGAAUUCAGUUCSUSCSAS - Chol -3', the whole chain 2'Ome modified	20 mg/kg dose, dissolved into 200 ul of PBS, with continuous injection of three days	tail vein	After SRS	Zhang et al. (2018) a
	KA	antagomir and agomir	x	1 nmol miR-146a agomir/1 nmol miR-146a antagomir	i.h.	After SRS	Li et al. (2018)
	KA	antagomir and mimic	x	mimic: single injection 5 or 10 μg in 1 μl; or repetitively (10 μg in 1 μl; one injection every three days for a total of five injections. antagomiR: was injected icv twice a day for six consecutive days (1 μg in 1 μl)	i.c.v.	Before SE and Early stages of epileptogenesis	Iori et al. (2017)
	PILO	inhibitor	x	1 nmol miR-146a inhibitor 2 h post-pilocarpine injection.	x	Early stages of epileptogenesis	Zhang et al. (2018) b
	PILO	inhibitor	miRNA-146a inhibitor (5'-AACCCAUGGAAUUCAGU UCUCA-3') or miRNA-146a mimics (5'-UGAGAACU GAAUUCCAUGGGUU-3')	1 nmol/10 μl	i.c.v.	Before SE	Huang et al. (2019)
	ELETRICAL STIMULATION	antagomir	x	20 nmol/ml (1 nmol/50 μl for each rat)	i.c.v.	Early stages of epileptogenesis	He et al. (2016)
	PILO	mimic	x	the miR-146a mimic solution (20 nmol/mL, 1 mL) was then administered via a pipette in 1μL drops, alternating between each naris every 2-3min	intranasal	Before SE	Tao et al., 2017
	PILO	mimic	x	10nmol of miR-146a-5p mimics in 5 μL of PBS	i.h.	Before SE and early stages of epileptogenesis	Deng et al. (2019)
134	KA	antagomir	Ant-134 (anti-mmu-miR-134; MW: 6127.3 Da); Exiqon, LNA-modified and 3'-cholesterol–modified oligonucleotides.	Mice were injected either IV or IP with 10 or 30 mg.kg-1.	mice were injected either IV or IP with 10 or 30 mg.kg-1 Ant-134	Early stages of epileptogenesis	Reschke et al. (2019)
	KA	antagomir	antagomirs targeting miR-134 (Ant-134: 5'-CC CCUCUGGUCAACCAGUCACA-Chol-3') (full length nucleotide 2'-methoxy modification, GenePharma, Shanghai, China)	0.12 nmol (in artificial cerebrospinal fluid at a speed of 0.2 μL/min)	i.c.v.	Early stages of epileptogenesis	Gao et al. (2019)
	KA	antagomir	LNA- and 3'-cholesterol modified oligonucleotides (Exiqon)	1 μl (0.12 nmol; Exiqon)	i.c.v.	Before SE	Rodriguez et al. (2017)
	PILO	antagomir	cholesterol-tagged LNA-antagomirs targeting miR-134 (Ant-134) (Exiqon A/S, Vedbaek, Denmark)	2 μl (0.12 nmol; Exiqon)	i.c.v.	Before SE	Jimenez-mateos et al. (2014)
	PILO	antagomir	x	2 μl (0.12 nM)	i.c.v.	early stages of epileptogenesis	Sun et al. (2017)
	KA	antagomir	Ant-134 LNA- and 3'-cholesterol modified oligonucleotides (Exiqon)	1 μl (0.12 nmol)	i.c.v. and intranasal	Before SE	Jimenez-mateos et al. (2012)
	PPS	antagomir	3'-cholesterol-tagged locked nucleic acid (LNA) oligonucleotide targeting miR-134 (Ant-134) (exiqon A/S, Vedbaek, Denmark)	0.36 nmol/6 mL	i.c.v	early stages of epileptogenesis	Reschke et al. (2017)

155	PILO	antagomir	x	0.12 nmol	i.c.v.	Before SE	Cai et al. (2016)
	KA	antagomir	x	1 nmol/10 µl	i.c.v.	early stages of epileptogenesis	Li et al. (2018)
	KA	antagomir	x	x	i.c.v.	early stages of epileptogenesis	Fu et al. (2019)
	PILO	antagomir	ant-155 was the chemically modified antisense oligonucleotide (Ant-155; RiboBio, Guangzhou, China)	1 nmol/5 µl	i.c.v	Before SE	Huang et al. (2018)
22	KA	antagomir	locked nucleic acid (LNA)- and 3'-cholesterol modified oligonucleotides. The miR-22 antagomir sequence was CTTCAACTGGCAGCT (purchased from Exiqon).	0.5 nmol/2 µl	i.c.v.	Before SE	Engel et al. (2017)
	KA	antagomir	MiR-22 inhibiting antagomirs (locked nucleic acid (LNA) and 3'-cholesterol modified oligonucleotides; sequence was CTTCAACTGGCAGCT. Purchased from Exiqon (Vadbaek, Denmark)	0.5 nmol/2 µl	i.c.v.	Before SE	Beamer et al. (2018)
	KA	knockout	heterozygous (miR–22+/-) and knockout (miR–22-/-)	x	x	X	Silva et al., 2020
	KA	antagomir and mimic	**Antagomirs** were from Exiqon (locked nucleic acid (LNA)- and 3'-cholesterol modified oligonucleotides). To **overexpress miR-22** we used chemically-modified double-stranded RNAs (mirVana™ mimics; Life technologies).	antagomiR (0.5 nmol/2 µL); mimic (0.5 pmol Mi22)	i.c.v.	Before SE (antagomir) and early stages of epileptogenesis (mimic)	Jimenez-Mateos et al., 2015
132	PILO	antagomir	x	5 µl/nmol	i.c.v.	Before SE	Huang et al. (2014)
	PILO	antagomir	x	1 nmol	i.c.v.	Early stages of epileptogenesis	Yuan et al. (2016)
	KA	antagomir	locked nucleic acid (LNA)-modified and 3' cholesterol-conjugated anti-miR-132 oligonucleotides (ie, antagomirs)	1.0 nmol/2 µL	i.c.v.	Before SE	Jimenez-Mateos et al., 2011
10a-5p	KA	antagomir	custom designed locked nucleic acid (LNA) oligonucleotide targeting: miR-10a-5p (antagomir sequence; capitals are LNA modifications - TCgGaTctACagGgT)	0.5 nmol/2 µl	i.c.v.	Before SE	Veno et al. (2020)
	KA	antagomir	locked nucleic acid (LNA) oligonucleotide targeting: miR-10a-5p//locked nucleic acid (LNA)-modified oligonucleotide miRNA inhibitors (antagomirs).	0.5 nmol/2 µl	i.c.v.	Before SE	Veno et al. (2019)
21a-5p	KA	antagomir	locked nucleic acid (LNA) oligonucleotide targeting: miR-21a-5p//locked nucleic acid (LNA)-modified oligonucleotide miRNA inhibitors (antagomirs).	0.5 nmol/2 µl	i.c.v.	Before SE	Veno et al. (2019)

	KA	antagomir	custom designed locked nucleic acid (LNA) oligonucleotide targeting: miR-21a-5p (TCaGtCtgATaaGcT)	0.5 nmol/2 µl	i.c.v.	Before SE	Veno et al. (2020)
23a	KA	antagomir and agomir	x	All injections were 1 ml and the injections were carried out over 60 s and the syringe was left in place for additional 2 min to minimize backflow after each injection.	i.c.v	early stages of epileptogenesis	Zhu et al. (2019)a
	KA	antagomir and agomir	x	The miR-23a agomir and antagomir obtained from Sangon Corporation (Sangon Biotech) were then i.c.v. injected 7 times at 2-day intervals.	i.c.v.	early stages of epileptogenesis	Zhu et al. (2019)b
27a-3p	KA	antagomir	locked nucleic acid (LNA) oligonucleotide targeting: miR-27a-3p//locked nucleic acid (LNA)-modified oligonucleotide miRNA inhibitors (antagomirs).	0.5 nmol/2 µl	i.c.v.	Before SE	Veno et al. (2019)
	KA	inhibitor	x	40 µl/day	i.p.	Before SE	Lu et al. (2019)
34a	KA	antagomir	x	0.1 or 0.5 nmol/2 µl	i.c.v.	Before SE	Sano et al. (2012)
	PILO	antagomir	x	20 nmol/mL (1 nmol/50 µL for each rat)	i.c.v	early stages of epileptogenesis	Hu et al. (2012)
124	KA	agomir	x	infusions of 0.25 nmol for a total of 1 nmol treatment.	i.c.v.	early stages of epileptogenesis	Brennan et al. (2016)
	PILO	mimic and inhibitor	miR-124 mimics and inhibitor were RNA duplex and were chemically modified and cholesterol conjugated from a hydoxyprolinol-linked cholesterol solid support and 2'-OMe phosphoramidites (provided by Guangzhou RiboBio Co., Ltd. (Guangzhou, China)	mimics (1 nM a total volume of 5µl); inhibitor (4 nM a total volume of 5µl) -	i.h.	Before SE	Wang et al. (2016)
142a-5p	KA	antagomir	custom designed locked nucleic acid (LNA) oligonucleotide targeting: miR-142a-5p (TGcTtTctACttTaT)	0.5 nmol/2 µl	i.c.v.	Before SE	Veno et al. (2020)
	KA	antagomir	locked nucleic acid (LNA) oligonucleotide targeting: miR-142a-5p/locked nucleic acid (LNA)-modified oligonucleotide miRNA inhibitors (antagomirs).	0.5 nmol/2 µl	i.c.v.	Before SE	Veno et al. (2019)
181a	PILO	antagomir	x	x	x	Early stages of epileptogenesis	Ren et al. (2016)
	PILO	antagomir	x	4 µL, 0.5 µL/min	i.c.v.	Before SE	Kong et al. (2020)
181b	PILO	antagomir and mimic	x	30µL of LV-rno-mir181b and LV-anti-181b-5p was injected	i.h.	early stages of epileptogenesis	Zhang et al. (2015)
	KA	agomir	x	10 nmol/kg was injected into the hippocampus of KA rats	I.C.V.	Early stages of epileptogenesis	Wang et al. (2019)
324-5p	PILO	antagomir	antagomir-324-5p LNA™-modified and custom-made by Qiagen (Hilden, Germany; formerly Exiqon)	0.5 nmol/2 µl	i.c.v.	After SRS	Tiware et al. (2019)
	KA	antagomir	All antagomirs were locked-nucleic acid-modified and obtained from Exiqon, Vedbaek, Denmark. For in	0.5 nmol/2 µl	i.c.v.	Before SE	Gross et al. (2016)

			vivo applications, a custom-made in vivo inhibitor (15 nucleotides) with a partial phosphorothioate backbone and no cholesterol tag (due to problems with synthesis and solubility) specific for miR-324-5p,				
21-5p	KA	antagomir	Ant-21-5p; Ribobio Guangzhou, People's Republic of China	1 nmol	i.c.v.	Before SE	Tang et al. (2018)
23b-3p	KA	agomir	x	x	i.c.v.	Before SE	Zhan et al., 2016
96	PILO	mimic	x	10 nmol	intracerebrally	Before SE	Gan et al. (2017)
129-5p	KA	antagomir	locked nucleic acid (LNA) oligonucleotide targeting miR-129-5p (anti-miR-129-5p)	0.5 nmol/2 µl	i.c.v.	Before SE	Rajman et al. (2017)
135a	KA	antagomir	antagomir-135a (ant-135a) LNA modified and 3'-cholesterol-modified oligonucleotides (Exiqon)	1.0 nmol/2ul	i.c.v.	Early stages of epileptogenesis	Vangoor et al. (2018)
137	PILO	antagomir and agomir	x	AGOMIR: 0.2 nmol/2 µL; antagomir: 0.8 nmol/2 µL	i.h.	Early stages of epileptogenesis	Wang et al. (2018)
139-5p	PILO	antagomir and agomir	x	1 nmol/50 µl for each rat	i.c.v.	early stages of epileptogenesis	Alsharafi et al. (2016)
142–5p	PILO	antagomir	5'aguagugcuuucuacuuuaug-Chol 3'	6 nmol/kg	i.c.v.	Before SE	Zhang et al. (2020)
145	PILO	antagomir	x	50 µL of drugs were evenly injected within 30 minutes	i.c.v.	Early stages of epileptogenesis	Zhao et al. (2019)
183	PILO	antagomir	x	1 nmol/50 µL	i.c.v	early stages of epileptogenesis	Feng et al. (2019)
187	PILO	antagomir	x	1 nmol/50µl for each rat	i.c.v.	early stages of epileptogenesis	Alsharafi et al. (2015)
199a-5p	PILO	antagomir	antagomir 199a (3'-cholesterol modified, 5'-phosphothiate modified) (GenePharma Shanghai, China)	1 nmol/5 µl per rat, infusion rate 0.5 µl/min	i.c.v.	Before SE	Wang et al. (2016)
200c-3p	PILO	inhibitor	x	2 µL and the injection rate of 0.25 µL/min	i.h.	early stages of epileptogenesis	Du et al. (2019)
203	PILO	antagomir	AM203 (2'-Omethylated-5'-cua gug guc cua aac auu uca c-3')	AM203 (5 nmol in 24 µL of 0.1 % v/v diethylpyrocarbonate-treated distilled water; Bioneer) was administered by pipette in 4-µL drops (a total of six fractions), alternating between each nostril every 2 min.	Intranasal	After SRS	Lee et al. (2017)
206	KA	agomir	x	10 nmol/kg (Co-injection miR-206 agomir with KA)	i.c.v.	Early stages of epileptogenesis	Wu et al. (2019)
210	PILO	inhibitor	x	1 nmol	i.h.	Early stages of epileptogenesis	Chen et al., 2016
211	PILO	transgenic	x	x	x	X	Bekenstein et al. (2017)
219	KA	antagomir and agomir	x	10 nmol/kg	i.c.v.	Early stages of epileptogenesis	Zheng et al. (2016)
431-5p	KA	antagomir	locked nucleic acid (LNA) oligonucleotide targeting: miR-431-5p//locked nucleic acid (LNA)-	0.5 nmol/2 µl	i.c.v.	Before SE	Veno et al. (2019)

			modified oligonucleotide miRNA inhibitors (antagomirs).				
494	PILO	agomir	x	1 nmol/50 µL	i.c.v.	Early stages of epileptogenesis	Qi et al. (2020)
let-7b	KA	mimic	x	6 µL of the AAV vector (3 µL at each location in the dorsal-ventral plane)	i.h.	Before SE	Han et al., 2020

Table 4. Neurobiological processes investigated in functional interference studies.

NEUROBIOLOGICAL PROCESS	Type of Functional interference				
	antagomir	inhibitor	mimic	agomir	genetic
Neuroinflammation (↓)	146a, 155, 181a-5p	146a, 27a-3p, 200c-3p	146a, let7b	206	x
Neuroinflammation (↑)	187, 22	x	x	146a, 124	x
Neurodegenaration (↓)	146a, 134, 155, 10a-5p, 21a-5p, 27a-3p, 34a, 132, 142a-5p, 181a, 324-5p, 21-5p, 129-5p, 142-5p, 145, 183, 199a-5p, 431-5p, 23a	146a, 27a-3p, 210, 200c-3p	96, 146a, 181b	206, 494, 181b	x
Neurodegenaration (↑)	181b	x	x	23a	x
Neurogenesis (↓)	x	x	x	x	x
Neurogenesis (↑)	22 (Beamer et al.,2018)	x	x	x	x
Gliosis (↓)	22 (microgliosis; Jimenez-Mateos et al., 2015) 134, 181a-5p	200c-3p	let7b	x	x
Gliosis (↑)	22 (astrogliosis; Jimenez-Mateos et al., 2015)	x	x	124	x
Axonal and dendritic plasticity (↓)	132, 134, 181a-5p	x	x	x	x
Axonal and dendritic plasticity (↑)	22	x	x	x	x
Cognitive function (↑)	134, 23a, 181a-5p, 21-5p, 145	x	x	181b	x
Cognitive function (↓)	22	x	x	23a	x
SE (↓)	146a (He et al., 2016), 134, 155, 10a-5p, 21a-5p, 132, 142a-5p, 324-5p, 21-5p, 129-5p, 142-5p, 183, 199a-5p, 431-5p	200c-3p	146a	23b-3p, 181b, 206, 219, 494	x
SE (↑)	146a (Iori et al., 2017), 219	x	x	x	211
SRS (↓)	132, 134, 155, 10a-5p, 21a-5p, 23a, 142a-5p, 324-5p, 135a, 203, 21-5p	27a-3p	22, 146a, 124, let7b	137	x
SRS (↑)	22, 137	124	x	146a	22, 211

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APÊNDICES

APÊNDICE A – Memorial Descritivo

MEMORIAL DESCRITIVO

Bruna Priscila dos Santos

A contingência do memorial

Este memorial descritivo tem como objetivo apresentar a minha trajetória acadêmica até o presente momento para conclusão do doutorado em Ciências da Saúde pelo Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Alagoas. Aqui, descrevi os elementos acadêmicos que fizeram parte da construção desta formação. Considero, portanto, este memorial um trabalho autoavaliativo, um instrumento confessional dos momentos de aprendizagem que ajudaram a concretizar mais uma etapa intelectual em minha vida.

SUMÁRIO

1 INTRODUÇÃO

Este memorial tem como objetivo descrever minha trajetória pessoal e acadêmica, onde busco pontuar minha formação, escolha profissional, direção dada a minha carreira, linhas de atuação e planos como professora e pesquisadora.

Desta forma, inicio a descrição da minha trajetória pessoal e que me levaram a trajetória acadêmica. Pois bem, desde criança, sempre fui muito curiosa, sempre quis entender como as coisas mais simples funcionavam, quem inventou, porque inventou. Durante minhas férias escolares, adorava ir às livrarias com meus pais para comprar os livros do novo ano escolar. Adorava o cheiro de livro novo, de folhear observando todas aquelas novidades, de ler na tentativa de compreender os fenômenos ali citados, alimentando minha curiosidade. Na adolescência não foi diferente, o meu interesse por entender como as "coisas" funcionavam, principalmente o corpo humano, em paralelo eu adorava ler sobre filosofia, sobre os pensamentos filosóficos e imaginar como eles chegaram às suas conclusões.

No ensino médio, essa curiosidade só aumentava e logo chegou ao momento em que eu deveria decidir qual curso superior eu gostaria de cursar e neste momento, lembro de ter feito um teste de aptidão e as minhas características indicavam a investigação científica, laboratorial. Comecei a pesquisar cursos que atendessem essa minha aptidão e então resolvi cursar biomedicina, pois era o curso que forneceria as habilidades necessárias para começar minha trajetória acadêmica/científica.

Em 2004, ingressei no curso de Biomedicina do Centro Universitário CESMAC, momento em que aprendi desde os conhecimentos básicos do corpo humano, assim como investigar suas alterações. Durante a graduação, aprendi as diversas possibilidades de investigação em ciências da saúde atrelada ao desenvolvimento do pensamento crítico. No entanto, durante este período, não fui incentivada a participar de projetos de pesquisa, iniciação científica, o que eu considero uma falha na minha formação enquanto biomédica (um dos motivos que me fizeram pensar em mudar esta realidade nas faculdades privadas). Assim que conclui minha graduação em Biomedicina, em 2009, a primeira oportunidade de emprego que tive foi a de instrutora de um curso técnico em Análises Clínicas e neste momento, comecei minha trajetória como professora. Apesar de não está inicialmente em meus planos ser professora, digo educadora, percebi o quanto aquele momento de transmissão de conhecimento junto aos meus estudantes me deixava feliz e completava de alguma forma a necessidade que eu sentia de modificar a realidade social através do conhecimento.

Iniciando minha vida profissional como professora/educadora, e acreditando que é uma das formas de mudar a realidade social, estimular o pensamento crítico, eu sentia falta do laboratório,

do trabalho investigativo, de alimentar minha curiosidade. Então, em meados de 2010, participei de uma seleção para estagiário voluntário no Laboratório de Biologia Celular e Molecular (LBCM) no então CCBI, atual ICBS, iniciando desta forma, minha trajetória científica.

Em 2011, fui aprovada na seleção de mestrado e passei a investigar pacientes com epilepsia através de aspectos clínicos e moleculares. Durante os dois anos em que passei no desenvolvimento do projeto de mestrado, tive a oportunidade de aprender sobre as dificuldades e alegrias de ser cientista/pesquisador no Brasil. Além disso, as oportunidades de aprendizagem aumentaram, participei de congressos, discussões cientificas, publicações de artigos científicos etc. Além disso, enfrentei desafios que me fortaleceram e fizeram acreditar o quanto aquele momento seria importante para minha formação acadêmica e contribuiria para um dos propósitos de vida, que é entender e ajudar a mudar uma realidade, neste caso, de pacientes com epilepsia. Após finalização do mestrado, em 2013, senti a necessidade da atuação/experiência enquanto biomédica atuando no diagnóstico laboratorial/análises clínicas.

Em 2014, iniciei minha atuação como biomédica assumindo o cargo de coordenadora de um laboratório municipal no interior de Alagoas. Durante este ano, eu segui minhas funções técnicas, mas sentindo falta de desenvolver novos projetos, de mudar uma realidade através do conhecimento e entendi que, somente o diagnóstico laboratorial não supria minha essência curiosa, eu queria atrelar a investigação ao diagnóstico. Aprender a ser cientista, a pesquisar e ensinar, era o que eu precisava para conseguir mudar realidades. Então, em 2015, participei da seleção para o doutorado e fui aprovada em primeiro lugar, reflexo de tudo aquilo que havia construído durante o mestrado.

Durante o doutorado, busquei cada vez mais aprender e aprimorar novas habilidades visando a meu futuro enquanto pesquisadora, levando em consideração que o conhecimento adquirido seria aplicado em qualquer área que eu decida ou tenha oportunidade de atuar enquanto cientista. E neste sentido, participei de diversas atividades acadêmicas desde a organização e participação de eventos, representação discente, discussões científicas, apresentações de trabalhos acadêmicos e principalmente, colaborei em projetos de iniciação científica e mestrado, tanto de alunos do mesmo laboratório quanto em outros laboratórios da UFAL, o que gerou frutos importantes como a publicação de artigos científicos, além de todas as experiências e conhecimentos adquiridos. Este ciclo de aprendizagem, portanto, encerra-se aqui, em 2020, quando defendo não só uma tese, mas uma trajetória acadêmica que não consigo dissociar da minha trajetória de vida.

2 IDENTIFICAÇÃO

- **Nome completo:** Bruna Priscila dos Santos
- **Filiação:** Claudia Lécia dos Santos e José Petrúcio dos Santos
- **Data e local de nascimento, nacionalidade:** Nascida em 29 de abril de 1986, em Arapiraca, Alagoas, Brasil.
- **Profissão:** Biomédica e Professora.
- **Cargo atual na carreira universitária:** Atualmente Coordenadora do Curso de Biomedicina da Faculdade Santa Bárbara e Professora da Faculdade Uninassau, ambas em Arapiraca, Alagoas.

3 FORMAÇÃO

- Graduação em Biomedicina, CESMAC, 2009.
- Graduação em Licenciatura Plena em Biologia, CESMAC, 2015;
- Especialização MBA em Auditoria em Serviços de Saúde, IBPEX, 2011;
- Mestrado em Ciências da Saúde, UFAL, 2013.

Para descrever minhas produções científicas e atividades acadêmicas, considerei o período entre 2015 a 2020, momento em que curso o Doutorado.

4 PRODUÇÃO CIENTÍFICA E/OU TECNOLÓGICA (2015-2020)

4.1 Relação dos trabalhos publicados

2015: *Lack of association between the prothrombin rs1799963 polymorphism and juvenile myoclonic epilepsy*. Autores: Born JP, Santos BP, Secolin R, Gameleira FT, Andrade TG, Machado LC, Gitaí LL, Gitaí DL. Periódico: Arquivos de Neuro-Psiquiatria. Impact factor: 1,160. Ano: 2015.

2017: *Genetic susceptibility in Juvenile Myoclonic epilepsy: systematic review of genetic association studies*. Autores: Bruna Priscila dos Santos, Chiara Rachel Maciel Marinho, Thalita Ewellyn Batista Sales Marques, Layanne Kelly Gomes Angelo, Maísa Vieira da Silva Malta, Marcelo Duzzioni, Olagide Wagner de Castro, João Pereira Leite, Fabiano Timbó Barbosa, Daniel Leite Góes Gitai. Periódico: Plosone. Impact factor: 2,740.

2017: *Functional Polymorphisms in the Neuropeptide S Receptor are not associated with Juvenile Myoclonic Epilepsy. Autores*: Chiara Rachel Maciel Marinho, Bruna Priscila dos Santos, Diego de Siqueira Figueredo, Ygor Daniel Ramos dos Santos, Livia Leite Góes Gitaí, Fernando Tenório Gameleira, Rodrigo Secolin, Marcelo Duzzioni, Olagide Wagner Castro, Tiago Gomes de Andrade, Daniel Leite Góes Gitai. Periódico: IJASRM. Impact factor: 5.015.

2018: *Lack of association between COMT Val158met polymorphism and Juvenile Myoclonic Epilepsy***.** International Journal of Advanced Scientific Research and Management (IJASRM). I.L, SILVA; SANTOS, B. P. et al. , v.3, p.21 - , 2018./ Impact factor: 5.015.

2020: *Caffeine improves various aspects of athletic performance in adolescents independent of their 163 C>A CYP1A2 genotypes.* SPINELI, HIGOR; PINTO, MARYSSA PONTES; DOS SANTOS, BRUNA PRISCILA et al. SCANDINAVIAN JOURNAL OF MEDICINE & SCIENCE IN SPORTS, v.30, p.959 - 1095, 2020./ Impact factor:3.255.

4.2 Relação de trabalhos apresentados em congressos e reuniões cientificas

2016: Papel funcional e potencial terapêutico do miR-352 em epilepsia experimental: efeitos in vivo da inibição de microRNA mediada por um Nanosistema. Autores: Santos, B.P; Araújo, M.A; Santos, Y.D.R; Santos Júnior, E.D; Correia, G.M.A; Dornelas, C.B; Gitaí, D.L.G. ***Evento: IV Workshop do Programa de Pós-Graduação em Ciências da Saúde***, realizado no Instituto de Ciências Biológicas e da Saúde, Local e data: UFAL, nos dias 13 e 14 de outubro de 2016.

2017: Identificação de novos microRNAs. Autores: Araújo, M.A; Santos, B.P; Santos, Y.D.R; Júnior, E.D; Paulino, P.A.T; Dornelas, C.B; Gitaí, D.L.G. ***Evento: V Workshop da Pós-Graduação em Ciências da Saúde e o I Seminário de Pós-Graduação da UFAL.*** Local e data: UFAL, 21 a 24 de novembro de 2017.

2018: Nanosistema Mg-Al-HDL para interferência funcional de microRNAs como potencial novo método terapêutico na epilepsia. Autores: Ygor Daniel Ramos dos Santos, Mykaella Andrade de Araújo, Bruna Priscila dos Santos, Erivaldo Davi dos Santos Júnior, Pedro Augusto Tibúrcio Paulino, Thayuanne Silva de Melo, Ênio José Bassi, Camila Braga Dornelas e Daniel Leite Góes Gitaí. ***Evento: XXII Encontro de Genética do Nordeste***, realizado de 27 a 30 de novembro de 2018, em Natal-RN.

2018: "Lack of association between COMT Val158met polymorphism and Juvenile Myoclonic Epilepsy" .Autores: SILVA, I.L; SANTOS JÚNIOR, E.D; SANTOS, Y.D.R; ARAÚJO, M.A; SANTOS, B.P; GITAI, D.L.G. ***Evento: International Symposium NEWroscience 2018***, Ribeirão Preto, from 18th to 21st September 2018.

5 ATIVIDADES ACADÊMICAS DESENVOLVIDAS

5.1 Apresentação de trabalhos e palestras

- Participação na comissão de organização do II Curso de Verão do Programa de Pós-graduação em Ciências da Saúde que ocorreu entre 23-28 de janeiro de 2017;

- Participação na comissão de organização do V Workshop da Pós-Graduação em Ciências da Saúde e o I Seminário de Pós-Graduação da UFAL que ocorreu entre 21-24 de novembro de 2017;
- Participação na XXXII Semana de Biologia do ICBS/UFAL - 04 e 06/09/2017, ministrando o minicurso intitulado: Identificação de genes de susceptibilidade em doenças complexas
- Participação na comissão de organização do III Curso de Verão do Programa de Pós-graduação em Ciências da Saúde que ocorreu entre 22-27 de janeiro de 2018.
- I Simpósio Internacional sobre Esclerose Lateral Amiotrófica-Maceió-AL, 03 a 05 de março de 2018.

5.2 Atividades de orientação de alunos e estagiários

1. **Orientação de alunos em iniciação científica:**
    a. **Alunos:** Gabriela Maria de Andrade Correia (bolsista); Erivaldo Davi dos Santos Júnior (colaborador); Ygor Daniel Ramos dos Santos (bolsista). **Projeto:** Síntese, caracterização e transfecção de nanocomplexos inibidores dos mirs-196b e 352 como ferramentas para estudos em epilepsia do lobo temporal. Data de início: 01/08/16-Data de conclusão: 31/07/17.

    b. **Alunos:** Ygor Daniel Ramos dos Santos (bolsista); Pedro Augusto Tibúrcio Paulino (bolsista); Erivaldo Davi dos Santos Júnior (colaborador); Thayuanne Silva de Melo (colaborador). **Projeto:** Efeito da inibição dos miRNAs 196b e 352 em modelo de epilepsia do lobo temporal. Data de início: 01/08/17-Data de conclusão: 31/07/18.

2. **Colaboração nos projetos abaixo listados:**
    a. **Título do projeto:** Associação entre os polimorfismos I/D da enzima conversora de angiotensina (ECA), C/A do CYP1A2, C/T do receptor A2A de adenosina (ADORA2A) e suplementação de cafeína sobre o desempenho aeróbio e anaeróbio em jovens atletas. **Aluno de Mestrado:** Higor Spineli**;** Local: PPGNUT/ UFAL**;** Defesa em: 06/07/2017.

    b. **Título do projeto:** Influência do polimorfismo da CYP1A2 e da suplementação de cafeína sobre o desempenho aeróbio e anaeróbio em jovens atletas. **Aluno de Mestrado:** Maryssa Pontes**;** Local: PPGNUT/ UFAL**;** Defesa em: 23/08/2017.

    c. **Título do projeto:** Identificação de microRNAs em epilepsia experimental e desenvolvimento de um nanosistema carreador de inibidores de microRNAs para ensaios funcionais. **Aluna de Doutorado**: Mykaella Andrade de Araújo. Defesa em 07/08/2018.

6. APROVAÇÃO EM CONCURSOS

a. Aprovação no concurso para Professor-monitor do Estado de Alagoas. Edital n°SEDUC nº 003/2018.

b. Aprovação no processo de recrutamento do Serviço Nacional de Aprendizagem - SENAC/AL, para instrutor. Edital n°SENAC/AL 01/2019.

c. Aprovação no concurso para Professor Substituto da Universidade Federal de Alagoas - UFAL, campus Arapiraca, área de atuação Morfologia, publicado no Diário Oficial do Estado de Alagoas, edição do dia 06/08/2019, edital n°43/2019, COPEVE.

Maceió-AL, 28 de novembro de 2020.

APÊNDICE B – Artigo 2015: *Lack of association between the prothrombin rs1799963 polymorphism and juvenile myoclonic epilepsy*

DOI: 10.1590/0004-282X20150010

ARTICLE

Lack of association between the prothrombin rs1799963 polymorphism and juvenile myoclonic epilepsy

Ausência de associação entre o polimorfismo G20210A (rs1799963) da protrombina e epilepsia mioclônica juvenil

João Paulo Lopes Born[1], *Bruna Priscila dos Santos*[1], *Rodrigo Secolin*[2], *Fernando Tenório Gameleira*[3], *Tiago Gomes de Andrade*[3], *Luciana Cláudia Herculano Machado*[4], *Lívia Leite Góes Gitaí*[5], *Daniel Leite Góes Gitaí*[6]

ABSTRACT

Juvenile myoclonic epilepsy (JME) accounts for 26% of generalized idiopathic epileptic syndromes. The highest levels of thrombin activity are closely involved in the development of neurological diseases, including epilepsy. The prothrombin c.20210G>A (rs1799963) variation, which alters prothrombin mRNA stability, is associated with high plasma prothrombin levels. Objective: The present study was designed to investigate whether the SNP rs1799963 is a risk factor for JME in the northeastern Brazilian population. Results: The polymorphism was genotyped in 207 controls and 123 patients using polymerase chain reaction-restriction fragment length polymorphism method. No significant differences were observed in the genotype and allele frequencies of this polymorphism between cases and controls. Conclusion: These results present no evidence for an association of rs1799963 with JME. Further studies including other types of epilepsy are required to investigate the involvement of prothrombin gene in the genetic susceptibility to chronic seizure.

Keywords: polymorphism, prothrombin, juvenile myoclonic epilepsy.

RESUMO

Epilepsia mioclônica juvenil (EMJ) representa 26% das síndromes epilépticas idiopáticas generalizadas. Níveis elevados de atividade da trombina estão intimamente envolvidos no desenvolvimento de distúrbios neurológicos, incluindo epilepsia. A variante c.20210G>A (rs1799963) do gene de protrombina, que altera a estabilidade do RNAm, está associada com altos níveis de protrombina no plasma. Objetivo: Investigar se o SNP rs1799963 é um fator de risco para EMJ em uma amostra da população do nordeste brasileiro. Resultados: O polimorfismo foi genotipado em 123 pacientes e 207 controles usando a reação de polimerase em cadeia com restrição de polimorfismo. Não observamos diferença significativa nas frequências alélicas e genotípicas deste polimorfismo, entre as populações de pacientes e controle. Conclusão: Estes resultados não demonstram evidências para uma associação do polimorfismo rs1799963 com EMJ. Estudos posteriores, incluindo outros tipos de epilepsia, são necessários para investigar o envolvimento do gene protrombina na susceptibilidade genética a crises crônicas.

Palavras-chave: polimorfismo, protrombina, epilepsia mioclônica juvenil.

Juvenile myoclonic epilepsy (JME) is a subtype of common idiopathic generalized epilepsy (IGE) and accounts for 10% of all forms of epilepsy and up to 26% of IGE. Onset is at puberty with equal sex ratio and it is characterized by myoclonic jerks, occasional generalized tonic-clonic seizures, and sometimes absence seizures[1]. It is also highly drug-dependent, since a

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The study was produced in Department of Cell, Molecular Biology and Genetic, Institute of Biological Sciences and Health, Federal University of Alagoas, Maceió, Alagoas, Brazil.

Conflict of interest: There is no conflict of interest to declare.

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APÊNDICE C – Artigo 2017: *Genetic susceptibility in Juvenile Myoclonic Epilepsy: Systematic review of genetic association studies*

PLOS ONE

RESEARCH ARTICLE

Genetic susceptibility in Juvenile Myoclonic Epilepsy: Systematic review of genetic association studies

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OPEN ACCESS

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

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Abstract

Background

Several genetic association investigations have been performed over the last three decades to identify variants underlying Juvenile Myoclonic Epilepsy (JME). Here, we evaluate the accumulating findings and provide an updated perspective of these studies.

Methodology

A systematic literature search was conducted using the PubMed, Embase, Scopus, Lilacs, epiGAD, Google Scholar and Sigle up to February 12, 2016. The quality of the included studies was assessed by a score and classified as low and high quality. Beyond outcome measures, information was extracted on the setting for each study, characteristics of population samples and polymorphisms.

Results

Fifty studies met eligibility criteria and were used for data extraction. With a single exception, all studies used a candidate gene approach, providing data on 229 polymorphisms in or near 55 different genes. Of variants investigating in independent data sets, only rs2029461 SNP in GRM4, rs3743123 in CX36 and rs3918149 in BRD2 showed a significant association with JME in at least two different background populations. The lack of consistent associations might be due to variations in experimental design and/or limitations of the approach.

APÊNDICE D – Artigo 2017: *Functional Polymorphisms in the Neuropeptide S Receptor are not associated with Juvenile Myoclonic Epilepsy*

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Functional Polymorphisms in the Neuropeptide S Receptor are not associated with Juvenile Myoclonic Epilepsy

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Abstract

It is largely accepted that the genetic susceptibility threshold is critical for Juvenile Myoclonic Epilepsy (JME) onset and probably reflects the simultaneous involvement of multiple genes with minor effect interacting with environment factors. The *NPSR1* encoding gene became a high-ranking candidate for epilepsy susceptibility, specifically considering a recent report of the proconvulsive effects of NPS in mice and that gain-of-function *NPSR1* polymorphisms were consistently associated with some epilepsy comorbidities, including sleep and anxiety. This case/control study was designed to investigate whether rs324981, rs2530547 and rs727162 *NPSR1* polymorphisms are associated with JME in the Brazilian population. The polymorphisms were genotyped in 97 JME patients and 193 control subjects by qPCR using TaqMan® SNP Genotyping Assays. Descriptive and statistical analyses were performed using SNPstats software. No significant differences were observed in the genotypic and allelic frequencies of these polymorphisms between cases and controls, even when analyses were restricted to endophenotypes. By Multifactor Dimensionality Reduction (MDR) analysis, we also tested for interactions between polymorphisms, comparing the patients with the control individuals. Even the allele composed by rs2530547C- rs324981A-rs727162C variants that correspond to a highly expressed (-103C) NPSR1 protein, characterized by increased signaling properties (107Asn and 241Ser), did not differ significantly between the groups. These results present no evidence for an association of these polymorphisms with JME. Further studies including other types of epilepsy and/or other functional polymorphisms are

APÊNDICE E – Artigo 2018: *Lack of association between COMT Val158met polymorphism and Juvenile Myoclonic Epilepsy*

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Lack of association between *COMT* Val158met polymorphism and Juvenile Myoclonic Epilepsy

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Alagoas, Brazil.

Abstract

Juvenile myoclonic epilepsy (JME) is the most common genetic generalized epilepsy, representing 5% to 10% of all epilepsies. The genetic component is an important factor in the etiology of JME, which may show Mendelian or genetically complex inheritance. Therefore, the identification of susceptibility genes for JME has aroused the interest of researchers. In this context, the gene encoding for the enzyme Catecholamine O-methyl Transferase (*COMT*), whose function is the deactivation of catecholamines in the synaptic cleft, is a strong candidate. The dysregulation of these neurotransmitters may contribute to the generation and modulation of seizures. Thus, the objective of this case/control study is to investigate whether the *COMT* val158met polymorphism (rs4680) is associated with JME. Genotyping of 96 patients and
200 controls was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and the statistical analyzes were done through the SNPStats platform. No significant differences were observed in the genotype and allele frequencies of this polymorphism between cases and controls. The results present no evidence for an association of *COMT* val158met with JME. Further studies including other functional polymorphisms are required to investigate the involvement of *COMT* gene in the genetic susceptibility to JME.

Keywords: *COMT, polymorphism, juvenile myoclonic epilepsy.*

1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common form of genetic generalized epilepsy. The frequency of JME is 5-10% of all people with epilepsy] (Jallon et al., 2005). JME typically manifests during adolescence and is characterized by arrhythmic myoclonic seizures, also experiencing generalized tonic-clonic seizures (GTCS) and, less often, absence seizures (ILAE., 1989).

JME have a complex genetic inheritance, making it difficult to identify susceptibility genes. In complex disorders such as these, interactions between different susceptibility genes may predispose to disease. A specific set of alleles in each determines the genetic threshold of susceptibility to a particular condition. In general, individuals with a high susceptibility threshold to epilepsy do not present epileptic seizures even when exposed to epileptogenic disorders or precipitating factors of seizures. On the other hand, individuals with low susceptibility threshold present chronic or reactive seizures when exposed, respectively, to epileptogenic disorders or precipitating factors of seizures. In order to obtain a synthetic view of the process of epileptogenesis, based on the above discussion, we can infer that epileptogenic disorders and precipitating factors, in a facilitating genetic environment, induce alterations in specific molecular pathways, which interfere, directly or indirectly, in the cerebral circuits, and may lead to the onset of epileptic seizures (Gitaí et al., 2008).

Thus, the identification of susceptibility genes helps to understand the genetic mechanisms involved in epilepsy. *COMT* is an essential gene controlling neural activity. This enzyme catalyzes the transfer of a methyl grouping of S-adenosylmethionine to catecholamines, which include dopamine, epinephrine, and norepinephrine. This mechanism interrupts the synaptic transmission exerted by these neurotransmitters. As epilepsy is related to

APÊNDICE F – Artigo 2020: *Caffeine improves various aspects of athletic performance in adolescents independent of their 163 C > A CYP1A2 genotypes*

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Caffeine improves various aspects of athletic performance in adolescents independent of their 163 C > A *CYP1A2* genotypes

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Purpose: The purpose of this study was to investigate whether variations in 163 C > A *CYP1A2* genotypes (rs 762 551) (AA, AC, and CC) modify the ergogenic effects of caffeine (CAF) on strength, power, muscular endurance, agility, and endur- ance in adolescent athletes.

Methods: One hundred adolescents (age = 15 ± 2 years) were recruited. Participants ingested CAF (6 mg.kg^{-1}) or placebo (PLA, 300 mg of cellulose) 1 hour before performing a sequence of physical tests: handgrip strength, vertical jumps, agility test, sit-ups, push-ups, and the Yo-Yo intermittent recovery test level 1 (Yo-Yo IR1).

Results: Compared to PLA, CAF enhanced ($P < .05$) sit-up (CAF = 37 ± 9; PLA = 35 ± 8 repetitions) and push-up repetitions (CAF = 26 ± 11; PLA = 24 ± 11 repetitions), and increased distance covered in Yo-Yo IR1 test (CAF = 1010.4 ± 378.9; PLA = 903.2 ± 325.7 m). There was no influence of CAF on handgrip strength (CAF = 35.1 ± 8.9; PLA = 33.7 ± 8.7 kgf), countermovement jump height (CAF = 49.3 ± 12.6; PLA = 47.9 ± 13.8 cm), spike jump height (CAF = 54.2 ± 13.6; PLA = 52.9 ± 14.5 cm), and time in agility test (CAF = 15.8 ± 1.1; PLA = 15.9 ± 1.3 s, $P > .05$). When present, the ergogenic effect of CAF was not dependent of genotype.

Conclusion: CAF improves muscular endurance and aerobic performance in adolescent athletes, regardless of their 163 C > A *CYP1A2* genotype.

KEYWORDS
caffeine, CYP, ergogenic effects, exercise, genetic polymorphism, teenagers