

## COMMENTARY

# Commentary on “Antiseizure activity by opioid receptor antagonism, new evidence”

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A major treatment modality of epilepsy consists of pharmacological interventions using small-molecule drugs that reduce the incidence and severity of seizures. In the last decades, efforts to discover these antiseizure medications (ASMs) have been dominated by a phenotypic approach using rodent seizure and epilepsy models. These efforts have resulted in the marketing of numerous small molecules that effectively treat the symptoms of the disease.<sup>1</sup> Unfortunately, a significant number of patients fail to achieve seizure freedom due to the occurrence of drug-resistant epilepsy (DRE), even when these ASMs are administered in combination.<sup>2</sup>

In an effort to find new molecules with an improved clinical efficacy profile, different research groups have taken different paths. An interesting approach is based on identifying compounds of interest using connectivity mapping (CMap, Broad Institute),<sup>3</sup> a database that provides the ability to compare the transcriptional profile of a disease with the gene expression signatures elicited by treatment of mammalian cells with these compounds. Highly similar or opposing expression signatures are termed connected and suggest disease- and compound-related physiological effects on mammalian cells. Thus, by querying a disease-related gene expression profile against the CMap database, one can find compounds with an expression profile that is opposite to the profile found for the disease, and that by reversing the genetic background of the disease, may improve the disease-related symptomatology. Importantly,

the database also includes approved medicinal products, which offers the possibility to bring repurposed therapeutics to the market, reducing the costs associated with traditional de novo drug development.

In previous work, a similar CMap-based strategy was used to identify compounds that could revert the diseased transcriptional profile of human tissue from epilepsy-affected brains. Next, a selection of compounds was functionally tested in a behavioral assay with zebrafish larvae and was found to suppress PTZ-induced seizures.<sup>4</sup> In the present follow-up study, Morgan Sturgeon and coworkers discovered that naltrexone, a compound previously found in the C-Map query, was able to decrease the abnormal locomotion of PTZ-treated zebrafish larvae and homozygous *scn1Lab* mutant (*scn1Lab*<sup>-/-</sup>) zebrafish.<sup>5</sup>

The latter mutant fish represent a model of Dravet syndrome (DS), a severe and highly drug-resistant developmental and epileptic encephalopathy, in the majority of cases due to *SCN1A* gene mutations, with onset of recurrent seizures during the first year of life of patients.<sup>6</sup> Of note, the zebrafish DS model was previously used to identify potential treatment options for Dravet syndrome<sup>7</sup> and to further decipher the mechanism of action of fenfluramine,<sup>8</sup> a therapeutic that together with cannabidiol is now considered second-line treatment for DS patients.<sup>9,10</sup>

In addition to the effects observed in the zebrafish models, naltrexone was also able to reduce in vitro neocortical seizure-like events in brain slices of adult WT mice, and to

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decrease in vivo the number and duration of PTZ-induced convulsive seizures in mice.

The results of the current study therefore confirm the possibility of using certain opioids as ASMs, at least in specific conditions. Naltrexone is presently used in the clinic for treating alcohol use disorder and manage opioid abuse.<sup>11,12</sup> The compound is considered a nonselective opioid receptor antagonist, although there is a significantly higher affinity for  $\mu$ -receptors than for  $\kappa$ - and  $\delta$ -receptors (Ki: 0.89 nM, 20.2 nM and 64.1 nM, respectively).<sup>13</sup> As a result, naltrexone has been found to produce a nearly complete blockade of  $\mu$ -receptors in humans at a dose of 50 mg/day, compared with 20% to 35% blockage of  $\delta$ -receptors.<sup>12</sup>

In previous studies, naltrexone has demonstrated anti-seizure but also pro-seizure effects at different doses using different animal models.<sup>5</sup> It is therefore tempting to think that the conflicting profile of the compound largely depends on the amount of different opioid receptors occupied, in combination with their relative distribution across different areas of the brain and the epileptic foci involved. In the current study, the homozygous *scn1Lab* mutant zebrafish larvae were exposed by immersion to 75  $\mu$ M naltrexone at 7dpf (days post-fertilization), but it is presently not known how much compound entered the brain, and what the affinity is for the zebrafish's individual opioid receptors. Future work could address these pending issues with the goal of further deciphering the mechanistic background of the results and translating the present findings to the clinic.

In conclusion, the data show that a combined CMap-zebrafish drug discovery strategy can be successfully applied to find antiseizure hits and identify novel pharmacological applications in the field of epilepsy.

### CONFLICT OF INTERESTS

I have no conflicts of interests to disclose. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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