

Identification of curcumin analogues with anti-seizure potential in vivo using chemical and genetic zebrafish larva seizure models

ABSTRACT

Seizures are the outward manifestation of abnormally excessive or synchronous brain activity. While seizures can be somewhat symptomatically managed with anti-epileptic drugs (AEDs), many patients are still refractory to the currently available AEDs. As a result, there is a need to identify new molecules with anti-seizure properties. Curcumin is the principle curcuminoid of *Curcuma longa*, or colloquially turmeric, and has been experimentally proven to have anti-convulsive properties, but its poor bioavailability has dampened further therapeutic interest. Hence, this study aimed to ask if structural analogues of curcumin with an adequate bioavailability could have an anti-seizure effect in vivo. To do so, we tested these analogues following a multipronged approach combining the use of several zebrafish seizure models (chemically-induced and genetic) and complementary assays (behavioural and brain activity). Overall, from the 68 analogues tested, we found 15 different derivatives that were able to significantly decrease the behavioural hyperactivity induced by pentylenetetrazol. Of those, only a few showed an effect on the hyperactivity phenotype of two genetic models of brain seizures that are the *gabral* and *gabrg2* knockouts. Two analogues, CA 80(1) and CA 74(1), were able to significantly alleviate brain seizures of *gabrg2*-mutant larvae. As a result, these analogues are good candidates as novel anti-seizure agents.

Keyword: Curcumin; Seizure; Anti-convulsive; Genetic epilepsies; Zebrafish