Possible explanation for neurotoxicity of BIA 10-2474 used in disastrous clinical trial

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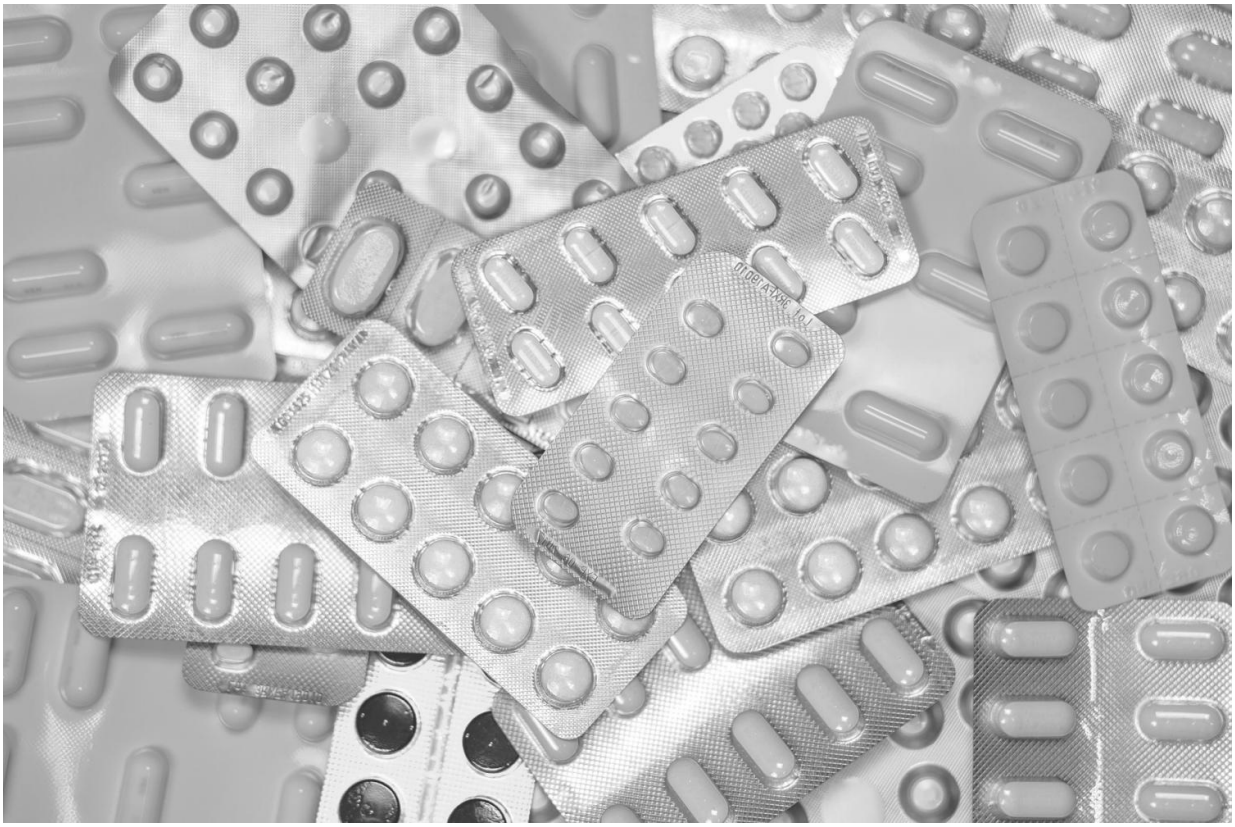

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(Medical Xpress)—A large team of researchers from the Netherlands, Italy and the U.S. has found a possible explanation for the injury and death to patients in a clinical trial held last year in France. In their paper

published in the journal *Science*, the team describes how they studied the impact of the drug on other enzymes and what they found by doing so.

Last year, researchers conducted a Phase I clinical trial in France to determine if a drug called BIA 10-2474 was safe for use in treating anxiety and other ailments. The trials resulted in six patients being hospitalized—one died and two were left with continuing neural problems. BIA 10-2474 was developed by pharmaceutical company Bial and the trials were run by a company called Biotrial. The drug was meant to treat ailments by inhibiting an enzyme called fatty acid amide hydrolase (FAAH). FAAHs in general are meant to do their work by breaking down endocannabinoids in the brain.

French officials looking into problems with the trials reported that neurotoxicity was likely due to off-target effects. In this new effort, the researchers sought to determine more specifically what those off-target effects might have been. They used activity-based protein profiling to search for other proteins that might have been impacted by the drug. They report that at high concentrations (which reflected the doses given to the patients in the clinical trials), the drug had an adverse impact on several lipases, which are enzymes involved in breaking down fatty acids . One of the lipases, the researchers note, was PNPLA6, which has been linked in prior work to genetic defects resulting in neurological disorders.

The research team readily acknowledges that their work does not prove that the neurotoxicity that occurred in the clinical trial patients was due to the off-target effects they found—they suggest sampling the brain of the patient who died to find out for sure. Also, it has been noted that Bial could and should have performed the same tests on the drug that were done in this new effort, as it has been noted that other pharmaceutical makers, such as Pfizer have done so with other FAAHs to prevent the kind of tragedy that occurred in the French clinical trial.

More information: Activity-based protein profiling reveals off-target proteins of the FAAH inhibitor BIA 10-2474, *Science* 09 Jun 2017: Vol. 356, Issue 6342, pp. 1084-1087, DOI: 10.1126/science.aaf7497 , science.sciencemag.org/content/356/6342/1084

Abstract

A recent phase 1 trial of the fatty acid amide hydrolase (FAAH) inhibitor BIA 10-2474 led to the death of one volunteer and produced mild-to-severe neurological symptoms in four others. Although the cause of the clinical neurotoxicity is unknown, it has been postulated, given the clinical safety profile of other tested FAAH inhibitors, that off-target activities of BIA 10-2474 may have played a role. Here we use activity-based proteomic methods to determine the protein interaction landscape of BIA 10-2474 in human cells and tissues. This analysis revealed that the drug inhibits several lipases that are not targeted by PF04457845, a highly selective and clinically tested FAAH inhibitor. BIA 10-2474, but not PF04457845, produced substantial alterations in lipid networks in human cortical neurons, suggesting that promiscuous lipase inhibitors have the potential to cause metabolic dysregulation in the nervous system.

Press release