Experimental obesity drug avoids brain effects that troubled predecessors

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Stockholm, Sweden: A second-generation experimental anti-obesity and diabetes drug has shown promise in reducing body weight in rodents just as effectively as the predecessor rimonabant while avoiding the risk of psychiatric side effects that led to the withdrawal of rimonabant from the market and stopped further development of other brain-penetrating drugs of its type.

The first generation of anti-obesity drugs that targeted the cannabinoid receptor CB1 - such as rimonabant - showed great promise as a therapy for obesity and related diseases such as diabetes. However, they were troubled by risk of psychiatric side effects. Rimonabant was withdrawn from the European market following a recommendation by the European Medicines Agency in late 2008, while further development of other similar products was halted.

However, in a study presented today (Monday) at the International Congress on Obesity in Stockholm, Sweden, Danish researchers demonstrated in rodents that a new first-in-class, second-generation CB1 receptor blocker induced the same degree of weight loss as rimonabant while not exposing the brain to significant levels of the drug. The drug was designed to act selectively in peripheral tissues and organs, in contrast with the first generation of CB1 receptor blockers, which also significantly affected the brain.

"These findings, together with what we have seen in our first human study regarding the safety and tolerability, make this drug candidate a

promising therapy for obesity and diabetes. The lack of significant exposure in the brain seen in our preclinical experiments provides optimism that blockade of the CB1 receptor may still be an effective and safe approach to treat obesity and related diseases," said Christian E. Elling, Vice President at 7TM Pharma A/S in Hoersholm, Denmark, who presented the findings at the conference. "This is, to our knowledge, the first peripheral CB1 drug candidate being tested in humans and these results indicate its development as a potential new treatment should be advanced."

In the rodent studies, the researchers conducted an extensive panel of studies with mice and rats to assess the weight-loss and anti-diabetic potential of the as-yet unnamed drug, TM38837, and to demonstrate the lack of exposure in the brain.

The researchers treated obese rats and mice with rimonabant, the new drug, or a placebo drug once a day for five weeks and measured their body weight and food intake daily. Animals lost an equal amount of body weight when treated with similar doses of rimonabant and TM38837. At the end of the treatment period, drug treated mice had 22-26% lower body weights than placebo treated mice while drug treated rats had 14% lower body weights than placebo treated rats.

Other animal studies provided substantial evidence that the drug has a markedly lower propensity than rimonabant to cross the blood-brain barrier. These studies included brain tissue examination, behavioural tests and other studies to demonstrate where in the body the drug was distributed.

For their human study of the drug, the researchers reported that in a phase 1 clinical trial of 48 healthy normal-weight adults, the drug was well tolerated even at the highest dose, with seven of the volunteers experiencing brief, mild drug-related side effects such as abdominal

discomfort, nausea and diarrhoea.

On the basis of these results, development of the drug is continuing. The researchers expect to report the results of further animal and human studies this autumn.

More information: The studies were funded by 7TM Pharma A/S.

Provided by International Association for the Study of Obesity