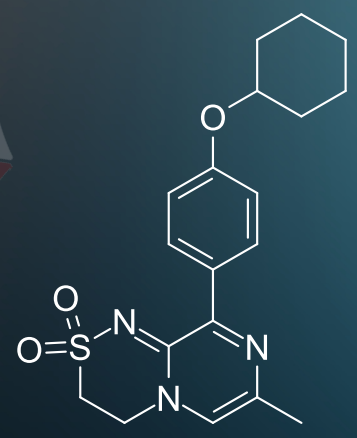

TAK-653 - A Novel Contender in the Fight Against Treatment-Resistant Depression

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History

TAK-653 was developed in the labs of the Takeda, a privately owned enterprise that was later transferred to Millennium Pharmaceuticals, who continued the development. The first scientific publications have been available only since 2020, no publicly accessible data exist before this date.

However, already in 2015, one human study phase II study was announced to investigate the effect of TAK-653 on patients with treatment resistant depression by Millennium Pharmaceuticals, but later withdrawn due to a business decision. However, later small scale trials were successfully completed. One further clinical study with over 100 estimated participants is currently in recruitment status.

TAK-653 is a positive allosteric modulator of the AMPA receptor, a type of the glutamate receptor. This receptor type is one of the main excitatory receptors in the central nervous system and plays a role in a wide range of cognitive functions. While TAK-653 does only minimally activate the AMPA receptor by itself, it does sensitize it for its natural glutamate ligand. This means lower glutamate concentrations are necessary to activate neuronal transmission, leading to an overall increased activity in the brain. TAK-653 is often trialed in conjunction with ketamine, which has anti-depressant effects connected to its modulation of AMPA receptor activity, in order to compare both compounds in effect strength.

TAK-653 has a close structural analog with similar effects with the name of TAK-137.

Animal Studies

A study focused on mechanistic aspects of TAK-653 and found that it activates the mTOR pathway in neurons and its upstream regulators. Animal experiments were also conducted and showed an antidepressant effect on rats treated with orally administered TAK-653 via water with a concentration of 5 mg/mL. Plasma level peaks were reached between 1 and 2 hours after administration of a total dose of 1 mg/kg. Plasma half-life of TAK-653 in rats was determined to be 1,9 hours. In contrast to ketamine, TAK-653 did no induce increased propensity for increased body movement at the therapeutic dosage.[1] This is likely due to the fact that ketamine also has effects on other receptors, most notably the NMDA glutamate receptor.

In the same study, TAK-653 also was found to significantly increased Brain-Derived Neurotrophic Factor (BDNF) protein levels in rats primary

cortical neurons. This compound protects neurons and their synapses and is involved in long-term memory formation. It can also promote the formation of new contacts between neurons which may be partially responsible for a effect on long - term memory.[2]

Administration of 0.3 mg/kg and higher doses up to 50 mg/kg of TAK-653 resulted in increased excitability of rats. TAK-653 concentrations in the brain of the animals were 3.53 ng/g for 0.3 mg/kg,

36.5 ng/g for 1 mg/kg, 210.6 ng/g for 8 mg/kg, and 264.2 ng/g for 50 mg/kg. This show brain concentrations do roughly linearly increase with ingested dose.[3] Another study on rats did show an increase on visual learning and memory at doses > 0.03 mg/kg taken orally (tested were 0.03, 0.1 and

0.3 mg/kg). Changes in social behavior were recorded as well. Interestingly, TAK-653 was also administered to monkeys in the same study at a dose of 0.06 mg/kg, who also showed cognitive improvements in working memory until up to 48 hours after administration. Only at a dose of 100 mg/kg TAK-653 one rat experiences long lasting convulsions at 4 hours after oral intake, indicating a seizure-promoting effect. This indicates that TAK-653 has a wide therapeutic range, with the harmful dose hundreds of times larger compared to effective dosing.[4]

Human Studies

In 2021, 24 healthy volunteers received 0.5 mg and 6 mg TAK-653 to asses the impact on Central Nervous System (CNS) excitability. Excitation of neurons with magnetic fields was easier when TAK- 653 was administered, which supports the hypothesis that TAK-653 lowers the threshold required for neurons to be activated.[3]

A recent study from 2022 on 24 more healthy volunteers investigated psychiatric effects of 0,5 mg and 6 mg TAK-653 taken orally. Patients did not report a feeling of a sensory “high”. Eye movement tracking experiments showed TAK-653 increased saccadic peak velocity, smooth pursuit and adaptive tracking at the time maximum plasma concentration was reached. This indicates increased CNS stimulation. The effects were more pronounced with 6 mg than with 0.5 mg TAK-653. Other neurological aspects, like influence on cognition were less pronounced, with no indication that short term cognitive function is altered in either dosage. No serious adverse effects were reported. Minor side effects were somnolence, headache and nasopharyngitis. No clinically significant effects on vital signs, ECGs or laboratory measurements were observed. Plasma half-life in humans was found to be between 33.1 and 47.8 hours.[5]

Conclusion

TAK-653 is a promising candidate for the treatment of depression that has previously been resistant to treatment with other drugs. At this time, ketamine is also explored for the same indication, but has the major problem of potential abuse and addiction, which has not been found to be present when using TAK-653. The anti-depressant like effects have so far only been shown in animals, so it remains unclear if TAK-653 will do the same in humans. A few human studies have been performed, but did not focus on depression but rather to explore generally excitatory components of the substance in the central nervous system. A clinical study in depressed patients is currently ongoing and is expected to be finished in the first quarter of 2024. TAK-653 may also increase short- and long-term cognitive functions in humans, indicated by experiments in rats and monkeys.

Collected data so far show a good safety profile with only minor side effects reported. Toxicological evaluation of animals also indicates large therapeutic windows, which means exceeding the recommended daily dose by multiple times would not be considered dangerous. The oral dose for humans used in studies to this date ranges between 0.5 mg and 18 mg per day. At very high doses, the risk of seizures is strongly increased.

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