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HOT TOPICS

Potentiation of AMPA receptors for rapid therapeutic gain in psychiatry has reached a new level of excitement

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A new age of antidepressants arose in 2006 with the publication of data describing the rapid-acting antidepressant effects of ketamine and scopolamine. These clinical findings led to the approval of (*S*)-ketamine for treatment-resistant depression in 2019 and a dextromethorphan/bupropion combination in 2022. The 2006 report of spirituality-evoking effects of psilocybin led to subsequent striking observations of rapid and enduring antidepressant effects of psyilocybin and other psychedelic drugs and the launch of numerous biotech companies. Clinical trial listings for ongoing studies with numerous other potential rapid-acting medicines (e.g., (*R*)-ketamine, esmethadone, zuranolone, psychedelics, mGlu2/3 receptor antagonists and NMDA receptor modulators) are prevalent [1].

AMPA receptors (AMPARs) are pivotal to the transduction of the antidepressant effects of conventional and rapid-acting antidepressants but have yet to be successfully utilized to generate a rapid-acting medication [2]. Potentiation of AMPARs by small molecules (AMPAkines) has raised neurotoxicity concerns, tolerability issues, and difficulties in identifying a potentiator with the optimal ability to energize (but not over-energize) excitatory neurotransmission. Although a Phase 1b study showed both mood and executive function improvements with the AMPAkine Org 26576, the development of this compound did not proceed. Clinical investigation of the AMPAkine TAK-653 in depressed patients is currently undergoing patient enrollment. TAK-653 has been studied in healthy volunteers where it demonstrated good tolerability and biological and antidepressant-associated biological activation [3]. There are also two Phase 2-ready AMPAkines under clinical development for sleep apnea, opioid-induced respiratory depression, and spinal cord injury (http://respirerx.com/product-pipeline/).

Recent advances in the pharmacology of AMPARs have brought us to a new starting point for making medicines. Discoveries into the molecular structure and function of AMPARs have broadly expanded the possibilities for the rationale design of novel compounds. Auxiliary proteins, such as the transmembrane AMPA receptor regulatory proteins (TARPS), are regionally localized in the brain where they can direct local changes in excitatory neurotransmission [4, 5].

The design of a rapid-acting antidepressant AMPAkine selectively targeting hippocampal AMPARs was suggested in 2006 [2]. Although such a compound has not yet been identified, the first TARP-selective AMPAR antagonist was generated, demonstrating proof-of-principle for modulation of distinct AMPAR populations [4]. Recently, docking studies of cryo-EM structures of GluA1/2-γ8 have identified novel binding and functional activity with both negative and positive allosterism [6]. Thus, compounds for modulating mood circuitry within the hippocampus through TARP-γ8-associated AMPARs may be available in the near future. The regional localization of this subset of AMPARs is predicted to impart efficacy without the ancillary effects of non-selective AMPAkines that act more diffusely across the brain as initially demonstrated for the TARP-γ8-selective antagonist [4].

In addition, the long-known cognitive enhancement produced by AMPAkines could be a value-added pharmacology for the cognitive impairment associated with depression. Thus, the potentiation of AMPARs for rapid therapeutic gain in major depressive disorder has reached a new level of excitement for which patients have long been waiting.

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JMW conceptualized the paper and both AL and JMW wrote and edited the manuscript.

COMPETING INTERESTS

The authors declare no competing interests. Both JMW and AL are employees of RespireRx Pharmaceuticals Inc. None of the compounds from this company are in clinical development for major depressive disorder.

ADDITIONAL INFORMATION

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