Special Lecture

Serotonin 5-HT1A receptor biased agonists: next generation treatments for serotonergic disorders

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Career

Neuroscience researcher with over 30 years' experience, Co-Founder and CEO of Neurolixis, a bioscience company developing clinical-stage drugs for treatment of neuropsychiatric and neurological disorders. Dr. Newman-Tancredi was previously Director of Neurobiology at Pierre Fabre Laboratories, identifying antidepressants, antipsychotics, and analgesic drug candidates. Prior to Pierre Fabre, he investigated signal transduction of monoamine receptors at the Servier Research Institute. He has published over 200 articles in peer-reviewed journals, is co-inventor on a dozen patents and serves as Councilor for the International Society for Serotonin Research. His principal current focus is the development of first-in-class serotonergic 'biased agonists' including befiradol (NLX-112), NLX-101 (F15599) and NLX-204. Dr. Newman-Tancredi previously characterized the pharmacology of several approved drugs, including milnacipran (Savella®), piribedil (Trivastal®), agomelatine (Valdoxan®) and levomilnacipran (Fetzima®).

Abstract

The treatment of central nervous system (CNS) disorders is undergoing profound change. Classic pharmacotherapies are increasingly considered inadequate in the face of the unmet medical burden of brain diseases. Although SSRIs and atypical antipsychotics are better tolerated than tricyclic antidepressants or typical antipsychotics, they do not show markedly improved therapeutic efficacy. Investigators are searching for more robustly active drugs, even if these necessitate increased medical care for patients. Examples of this trend are the use of ketamine and psychedelic compounds for treatment-resistant depression and other neuropsychiatric conditions. Interestingly, the mechanism of action of these drugs involves the activation of serotonergic systems in specific brain regions, notably in cortex. Moreover, the antidepressant effects of ketamine and (probably) psychedelics drugs involve activation of 5-HT1A receptors, suggesting that these constitute promising targets for development of improved CNS drugs. However, the development of drug candidates that activate 5-HT1A receptors has proved challenging: there are currently no approved selective and high efficacy agonists for clinical use. There is therefore increasing interest in novel, highly selective serotonin 5-HT1A receptor compounds that show 'biased agonist' activity at subpopulations of receptors in different brain regions. NLX-101 shows preferential activity at 5-HT1A heteroreceptors in cortical regions associated with control of mood and cognition, whereas NLX-112 has more pronounced activity at 5-HT1A autoreceptors in the Raphe nuclei associated with control of motor dysfunction. These diverging profiles translate to distinct in vivo behavioral effects and therapeutic indications. Accordingly, NLX-101 is in development as a potential treatment for autism spectrum disorders, whereas NLX-112 is being developed for treatment of movement disorders. A novel drug candidate, NLX-204 shows exceptional antidepressant-like properties in rodent models, equivalent to those of ketamine. Taken together, these findings suggest that a new generation of serotonin 5-HT1A receptor agonists will become available for improved treatment of disorders involving serotonergic neurotransmission.