

Does Central Serotonin_{2C} Receptor still have New Therapeutic Potential?

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Since the 1950s, when serotonin (5-HT) was discovered in the mammalian central nervous system (CNS), an enormous amount of experimental evidence has revealed the pivotal role of this biogenic amine in a number of cognitive and behavioural functions [1]. Although 5-HT is synthesized by a small group of neurons within the raphe nuclei of the brain stem, almost all parts of the CNS receive serotonergic projections. Furthermore, the importance of 5-HT modulation and the fine-tuning of its action are underlined by the large number of 5-HT binding sites found in the CNS. Hitherto, up to 15 different 5-HT receptors subtypes have been identified [2]. Large amounts of experimental evidence have explored the pathophysiological role of one of these receptors, the 5-HT_{2C} receptor, that has emerged as a prominent central serotonin receptor subtype [3]. Indeed, since its discovery about 25 years ago by Palacios, Pazos and Hoyer, who named it 5-HT_{1C} [4] (see the book 5-HT_{2C} Receptors in the Pathophysiology of CNS disease, 2011); it has been shown to play a major role in the regulation of a plethora of behaviours. Therefore, it is not surprising that experimental and clinical observations have highlighted it as a possible therapeutic target for the development of drugs for a range of CNS disorders such as schizophrenia, depression, drug abuse, eating disorders, Parkinson's disease and epilepsy, to cite but a few [5-10]. Thus, the 5-HT_{2C} antagonism appears to be an important feature of antipsychotic and antidepressants drugs with broad pharmacological profiles, properties that probably contribute to the treatment of negative and depressive symptoms respectively, or to the mitigation of side-effects. Although several selective agents for this receptor have been discovered, none have reached the market for the treatment of CNS disorders to date, essentially as a result of their limited efficacy and related side effects. Indeed, most of the 5-HT_{2C} ligands have binding affinity for the 5-HT_{2B} receptors, which may limit its therapeutic potential given that action at peripheral 5-HT_{2B} receptors is thought to underlie the cardiopulmonary complications associated with some serotonergic drugs [11]. Several pharmaceutical companies are still very active in 5-HT_{2C} receptors research. Nevertheless, the only compound with 5-HT_{2C} affinity that has reached the market is agomelatine, released by Servier for the treatment of major depressive disorder with a reduced level of sexual side effects compared to some other antidepressants. Agomelatine is a melatonergic agonist (MT₁ and MT₂ receptors) and 5-HT_{2C} antagonist [12]. Probably the next 5-HT_{2C} compound to obtain the Food and Drug Administration (FDA) approval in the United States will be lorcaserin by Arena Pharmaceuticals, for the treatment of obesity [13]. Lorcaserin shows 100 times higher affinity for 5-HT_{2C} versus other receptors, the only drawback is the exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma. However, given the results of the Pathology Working Group, this may no longer be of concern since there is no statistically significant increase in mammary risk for lorcaserin patients. Therefore there is good chance for lorcaserin to gain the FDA approval later on during this year.

There are also many avenues that remain unexplored, so there are undoubtedly further advances to be made. For example, we are currently carrying out some experiments on the effect of 5-HT_{2C} ligands in

different models of epilepsy both generalised and focal seizures and we have obtained very promising results. Our preliminary data show that agonists for the 5-HT_{2C} receptors have a potent antiepileptic action. These findings are in agreement with the well known activity of 5-HT_{2C} receptor signal in controlling cell excitability [14]. Indeed, mice knock out for this receptor have higher rate of mortality and the survived ones show an increased susceptibility to seizures [14-17]. Although the available compelling evidence for the role of 5-HT_{2C} receptors in epileptogenesis and/or propagation, no drugs are currently under development by pharmaceutical companies. This reflects a general situation of lack of investment by the pharmaceutical industry in research for CNS diseases, especially for epilepsy. Even in high-income countries, epilepsy has suffered historical neglect and despite high costs and severe disabling effects, epilepsy may attract somewhat less research funding from public and private sources than other less common chronic neurological disorders. To bring to the market new drugs, the relation between the epilepsy community and pharmaceutical companies must change. Indeed, governments should understand that basic and clinical academic epilepsy research particularly needs independent support to overcome the natural tendency of the drug industry to prefer markets with a larger monetary value. Therefore, increasing funding for public laboratories is of paramount importance.

Nevertheless, I am hopeful that in the next few years, we certainly will see new compounds selective for 5-HT_{2C} receptors, making further significant impacts on the treatment of the major neuropsychiatric disturbances, including epilepsy. In conclusion, it is apparent that 5-HT_{2C} receptors still offer therapeutic potential, even those not yet discovered.

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