Novel approaches to drug design for the treatment of schizophrenia

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ABSTRACT

Schizophrenia is an important health issue affecting almost 1% of the population withsignificant unmet medical needs. The classical drug targets for the treatment of schizophrenia are dopamine D2 receptors.Second generation ("Atypical") drugs block more receptors of the GPCR class 1 (e.g. Clozapineis a D(2)-5HT(2) antagonist). Here, new targets for GPCR as well as ligand-gated ion channelsare presented. An analysis of the opportunities for drug design offered by the structures solvedrecently is also presented. For drug design the availability of these protein structures, or the possibility to build highquality models, allows to shift the paradigm from ligand-based to target-based drug design. Theanalysis of drugs on the market and under development shows that numerous targets are beingconsidered which may reveal anambiguity on the ideal drug target. This situation might besimplified in the future thanks to integrative projects started recently: the 'Human Brain Project'and the 'Brain Activity Map' that aim at modeling the brain as well as the Allen Atlas. G-Protein Coupled Receptors and Ligand-Gated Ion Channels are potential targets to treat Schizophrenia. Structures have become available in the recent years for most of LGIC and GPCR receptors that are potential targets to treat schizophrenia.Structurebased drug design is tractable on these receptors.GPCR and LGIC are allosteric proteins.Integrative projects may help discriminate between the numerous potential targets in thefuture.

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