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Minireview

Screening the receptorome for plant-based psychoactive compounds

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Abstract

Throughout time, humans have used psychoactive plants and plant-derived products for spiritual, therapeutic and recreational purposes. Furthermore, the investigation of psychoactive plants such as *Cannabis sativa* (marijuana), *Nicotiana tabacum* (tobacco) and analogues of psychoactive plant derivatives such as lysergic acid diethylamide (LSD) have provided insight into our understanding of neurochemical processes and diseases of the CNS. Currently, many of these compounds are being used to treat a variety of diseases, such as depression and anxiety in the case of *Piper methysticum* Kava Kava (Martin et al., 2002; Singh and Singh, 2002). G-protein coupled receptors (GPCRs) are the most common molecular target for both psychoactive drugs and pharmaceuticals. The "receptorome" (that portion of the genome encoding ligand reception) encompasses more than 8% of the human genome (Roth et al., 2004) and as such provides a large number of possible targets for psychoactive drug interactions. A systematic, comprehensive study is necessary to identify novel active psychoactive plant-based compounds and the molecular targets of known compounds. Herein we describe the development of a high throughput system (HTS) to screen psychoactive compounds against the receptorome and present two examples (*Salvia divinorum*, the "magic mint" hallucinogen and *Banisteriopsis caapi*, the main component of Ayahuasca, a psychoactive beverage) where HTS enabled the identification of the molecular target of each compound.

Keywords: GPCR; Salvinorin A; Ayahuasca

Contents

Introduction

Psychoactive plants exert profound effects on human consciousness, emotion, and cognition, and as such have been used by humans throughout time for recreational, spiritual, and therapeutic purposes (Lewin, 1924). *Cannabis sativa* (marijuana), *Papaver somniferum* (opium), *Coffea arabica* (caffeine), *Nicotiana tabacum* (tobacco), as well as other plants and plant-derived substances are widely used and abused at present. Investigation of psychoactive plants and their mechanisms of action have provided insight into the neurochemistry of many CNS diseases as well as the "chemistry of consciousness" (Lewin, 1924; Nichols, 2004). The observation that

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serotonin and lysergic acid diethylamide, the analogue of ergot alkaloids produced by *Claviceps purpurae*, share structural and pharmacological properties led to the suggestion that biogenic amines, like serotonin, were involved in mental disorders such as schizophrenia (Gaddum and Hameed, 1954; Wooley and Shaw, 1954). Additionally, the active ingredient in *Rauwolfa serpentina* (resperine) has been shown to deplete biogenic amines and induce depression, therefore suggesting that a lack of serotonin and/or norepeinephrine may be the cause of this pathology (Vertulani and Sulser, 1975). Our basic understanding of mental illness as a neurochemical disease, as well as our ability to treat these disorders has been greatly enhanced through the study of psychoactive plants. Continued evaluation of the molecular site of action of psychoactive drugs will expand our list of validated targets for CNS drug discovery.

Plants and plant-derived psychoactive compounds exert their actions via interaction with various signal transduction molecules, either a cell surface or intracellular recognition molecule (i.e. 'receptors'). It has recently been estimated that ~20% of the recently completed human genome sequence is devoted to signal transduction, and specifically receptors (Lander et al., 2001; Venter et al., 2001). Sequencing the genome therefore, revealed a large number of potential targets for psychoactive drugs, and suggested the necessity of a comprehensive, systematic approach to identifying such targets. As summarized below, the development of high throughput screening (HTS) tools are necessary to screen psychoactive compounds against the receptorome.

The receptorome

Of the relatively large portion of the human genome dedicated to signal transduction, that portion dedicated to encoding ligand reception has been described as the "receptorome" (Kroeze et al., 2003) and encompasses more than 8% of the human genome (Roth et al., 2004). The receptorome is subdivided into multiple receptor superfamilies, the largest of which is that of the G-protein coupled receptors (GPCRs). The GPCR superfamily accounts for approximately 3.7% of the human genome: 735–802 open reading frames, of which ~375 are neither olfactory nor taste receptors (Fredriksson et al., 2003; Kroeze et al., 2003; Roth et al., 2004). GPCRs are the most common molecular target for psychoactive drugs and pharmaceuticals (Hopkins and Groom, 2002; Kroeze et al., 2003; Lander et al., 2001; Vassilatis et al., 2003). Non-GPCR receptors represent at least 1.5% of the genome (Venter et al., 2001). Naturally occurring psychoactive compounds may also produce responses via ion channels and transporters, functioning as "receptors," which represent an additional 3% of the genome (Roth et al., 2004; Venter et al., 2001).

Receptoromics

Virtual screening of the receptorome

Multiple computational resources currently exist to assist in screening psychoactive compounds against the receptorome in a virtual (in silico) manner. Bioinformatic approaches such as BLAST have provided information on ligand:receptor interaction based on consensus domain profiling and hidden Markov models (HMM) (Gaulton and Attwood, 2003; Wise et al., 2004). Molecular modeling has also been used to virtually screen libraries of compounds for drug discovery efforts. For most GPCR, this classical computational approach has utilized homology modeling with rhodopsin (Ballesteros et al., 2001; Palczewski et al., 2000; Shapiro et al., 2002). This model has been quite successful in identifying molecular targets on the 5-HT_{2A} receptor, which interacts with many plant-derived hallucinogens (e.g., lysergic acid amide, psilocybin, mescaline) (Nichols, 2004; Roth et al., 2004). Molecular visualization software such as RasMol (http://www.umass.edu/microbio/rasmol) is another useful tool for viewing structure:function relationships and may be accessed for free.

Multiple on-line resources for identifying molecular targets for psychoactive botanicals also exist, and provide information for scientists and nonscientists alike (Table 1). Both *The Vaults of Erowid* (http://www.erowid.org) and *The Lycaeum* (http://www.lycaeum.org) provide useful background on the chemistry, molecular targets, history and lore of psychoactive plants. Although these sites are not subject to peer review, they do provide useful information to the interested nonscientist such as anecdotal user reports, botanical information and links to additional articles.

Databases, such as the National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH-PDSP) K_i Database (http://kidb.cwru.edu), allow users to quickly identify

Table 1
Representative on-line resources for screening the receptorome

Name	URL	Type of information
NIH Blast	http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/information3.html	MM, S
Rasmol	http://www.umass.edu/microbio/rasmol/	MM
The Vaults of Erowid	http://www.erowid.org/	A,B,C,L,MT
Entheogen dot	http://www.entheogen.com/	A,C,MT
The Lycaeum	http://www.lycaeum.org/	A,B,C,L,MT
Botanical.com	http://www.botanical.com/	B
Multidisciplinary association for psychedelic studies	http://maps.org/	L
Heffter Research Institute	http://www.heffter.org/	C,L,MT
NIMH-PDSP database	http://kidb.cwru.edu/	C,L,MT

A = anecdotal user reports; B = botanical information; C = chemistry; L = links to articles; MM = molecular modeling or visualization; MT = molecular target; S = sequencing information.