new hot papers - 2010

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Jeffrey Conn talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Pharmacology &Toxicology.

Article Title: Allosteric modulators of GPCRs: a novel approach for the treatment of CNS disorders
Authors: **Conn, PJ**;Christopoulos, A;Lindsley, CW
Journal: NAT REV DRUG DISCOV, Volume: 8, Issue: 1, Page: 41-54, Year: JAN 2009
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SW: Why do you think your paper is highly cited?

G-protein-coupled receptors (GPCRs) have been among the most successful of drug targets and are involved, in a fundamental way, in regulating virtually every cellular or organ system. However, there has been an impasse for many years in the discovery and development of highly selective small molecule ligands for several GPCR subtypes.

In recent years, there has been a fundamental advance in developing highly selective activators and inhibitors of many previously intractable GPCR subtypes by discovery of allosteric modulators that target sites other than the normal neurotransmitter or hormone binding site.

In addition to providing high selectivity, these compounds provide multiple modes of efficacy that can provide much more subtle control of GPCR function. This is having a major impact on multiple research areas, both by providing new tools and a new approach to developing therapeutic agents.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

It summarizes studies that are leading to a fundamental shift in our thinking and provides a synthesis of knowledge that has been developing over the last five to seven years.

SW: Would you summarize the significance of your paper in layman's terms?

Many marketed drugs act on a class of drug targets that serve as specific receptors for neurotransmitters. These traditional drugs act as on/off switches to either activate or inhibit the activity of the receptor. However, this "all-or-nothing" action can often lead to unwanted side effects. Also, it has been difficult to develop drugs that only act on one receptor and not on others.

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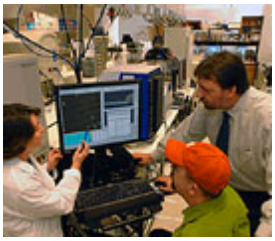

Jeffrey Conn Research Group at Vanderbilt.

Discovery of novel drug-like molecules, termed allosteric modulators, provide a new approach to developing drugs that act as "dimmer switches," to have more subtle effects that either increase or decrease the activity of specific neurotransmitter receptors, and thereby, fine-tune their activity in such a manner may offer better efficacy, without the same side effects.

Also, these new molecules have been much more selective for individual receptor subtypes than have many drugs developed using traditional approaches.

SW: How did you become involved in this research, and were there any problems along the way?

I had spent many years trying to develop highly selective agents that act on individual GPCR subtypes. Highly selective agents for the receptors we study proved to be impossible to develop. This prevented us from establishing the physiological roles of these receptors and made them intractable as drug targets.

We began to reason that the lack of ability to develop highly selective compounds was likely due to the high level of conservation of the neurotransmitter binding site across receptor subtypes.

Based on this, we reasoned that we may be able to develop more selective compounds by moving away from the normal neurotransmitter binding site and developing allosteric modulators.

This approach was highly successful, and we and other groups have now developed highly selective allosteric modulators for multiple GPCR subtypes. This paper is a review of studies by multiple scientists in this field.

SW: Where do you see your research leading in the future?

This research is leading to fundamental advances in multiple areas, including our understanding of the mechanisms of GPCR signaling, mechanisms involved in regulation of multiple cell and biological systems, and novel approaches to treatment of human disease.

There are now two allosteric modulators that are marketed for treatment of human disorders.

These are cinacalcet (Sensipar®; Amgen). This is a positive allosteric modulator (PAM) of the calcium-sensing receptor (CasR), which increases sensitivity to circulating calcium. CasR is involved in the regulation of calcium homeostasis and renal calcium resorption and cinacalcet is used for treatment of hyperparathyroidism.

More recently, maraviroc (Celsentri®; Pfizer), a negative allosteric modulator (NAM) of the chemokine receptor CCR5, was launched for the treatment of HIv infections. Maraviroc binds to CCR5, stabilizing a receptor conformation that has lower affinity for the HIV virus, thereby blocking CCR5-dependent entry of HIV-1 into cells.

There are multiple metabotropic glutamate receptor 5 (mGluR5) NAMs in clinical development but none are on the market. In the future, this is likely to develop even further for multiple disorders.

Also, we are now establishing compounds which selectively modulate coupling of receptors to some, but not all, signaling pathways. This is likely to be a major focus of future studies. It will provide information about specific signaling systems involved in regulating different physiological responses and more specific targeting of individual signaling pathways for the development of therapeutic agents.

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