Combating mood disorders: New approach simplifies the search for more specific drugs

September 30 2011

Many psychiatric conditions are caused by aberrant metabolism of the neurotransmitter serotonin. Researchers in the Department of Pharmacy at LMU have now developed a new screening method, which will facilitate the search for new drugs that modulate the biological activity of serotonin.

Psychiatric ailments such as depression, obsessive-compulsive disorder or anxiety states are often associated with disturbances in the metabolism of the neurotransmitter serotonin. Neurotransmitters are compounds that are released from the synapses at nerve cell endings and activate the firing of neighboring neurons. Thus, as their name suggests, they mediate the transmission of nerve impulses. The serotonin transporter (SERT) is responsible for reuptake of the transmitter into neurons, terminating its action. SERT is a major target for drugs that are used to treat many mood disorders, and the search for new SERT inhibitors is of continuing therapeutic relevance. A research team led by Professor Klaus Wanner of the Department of Pharmacy in the Center for Pharmaceutical Research at Ludwig-Maximilians Univeristät München (LMU) has now developed a novel binding assay, based on the use of mass spectrometry (MS), which promises to simplify the search for potential SERT inhibitors very significantly. The major advantage of the technique is that, unlike conventional binding assays, it avoids the need to use radiolabeled substances. A paper that describes the new assay will appear in the journal *ChemMedChem* on 4. October. The article has been rated as a "very important paper" and is featured on the cover of the upcoming issue of the journal.

To be effective, most drugs must bind selectively to defined molecular targets in the body. The target may be an enzyme found in certain cells or a protein on the plasma membrane of a specific cell type. Drug candidates must therefore be assessed for their affinity for the target by means of binding assays. These assays often involve the use of a chemical that is already known to recognize and bind selectively to the target as. The ability of a test substance to find and interact with the target is then measured in terms of how well it competes with this "marker" ligand. The greater its ability to displace the marker from the binding site, the higher is its own affinity for the target, and the more likely it is to be clinically effective. In the MS-based binding assay developed by Wanner's group, quantification of the marker is carried out using mass spectrometry. In contrast to conventional techniques, which employ radiolabeled ligands, MS binding assays do not require the use of markers containing radioactive isotopes. This means that the marker can be assayed in its unaltered, native state. "This label-free technique provides all the advantages offered by classical binding studies, while avoiding the need to work with radioactive compounds," explains Wanner. His team has now validated the MS-based binding assay for use in the search for new inhibitors of SERT function. "Because SERT regulates the concentration of serotonin in the synaptic cleft, the protein serves as the major target for the treatment of depression, obsessive-compulsive disorders and anxiety states," says Wanner. Using the well-known antidepressant (S)-fluoxetine as a native marker, his group has now shown that the results of the MS-based assay are in very good agreement with those obtained using radiolabeled ligands. Indeed, the team now routinely uses the MS method to screen for novel, pharmacologically active SERT inhibitors. In addition, Wanner has plans to adapt the approach for use with other target molecules of clinical interest. (göd)

More information: (S)- and (R)-Fluoxetine as Native Markers in Mass Spectrometry (MS) Binding Assays Addressing the Serotonin

Transporter.
M. Hess, G. Höfner, K. Wanner. *ChemMedChem* 2011, vol 6, no. 10, 4. October; First published online 26. July 2011
doi:10.1002/cmdc.201100251