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Insight from brain scans helps hone the use of antipsychotic medication

The majority of people with schizophrenia are, at some time after diagnosis, prescribed antipsychotic drugs, medication given not to cure, but to alleviate the symptoms of psychosis – hallucinations, delusions, agitation and confusion.

No one fully knows, however, how the family of drugs used as antipsychotic medication achieve their effects. Just as scientists do not yet have a complete picture of what happens inside the brain to cause the symptoms of psychosis, they do not yet have a full understanding of the mechanisms of antipsychotic drugs, also called neuroleptics.

There are about two dozen different types of antipsychotic medication, all of which alter the levels of chemicals inside the brain. The first were used in the 1950s and both this original generation of drugs (called typical antispsychotics) and a second generation used since the 1990s (atypical) can cause side effects in a significant number of patients. These include drowsiness, muscle stiffness, a dry mouth, shaking, restlessness, increased appetite, blurred vision and sexual difficulties, and are often one of the reasons why people stop taking their medication.

Understanding more about how and where the medications interact with the natural chemicals inside the brain can help doctors refine dosages and use existing drugs in a more effective way, with fewer resulting side effects.

Researchers already know that the abnormal production of too much of the brain chemical dopamine can lead to hallucinatory experiences, delusions and disordered thoughts. The chemical structure of antipsychotic medication allows it to bind with dopamine receptors and block their function. It seems that by stopping the transmission of dopamine from one nerve cell to another, the drugs dampen these symptoms.

But does the medication stand in the way of other neurotransmitters, in addition to dopamine? Which receptors do they block, and in which parts of the brain? Do the drugs block too many receptors? Are some receptors they bind linked to other receptors in different parts of the brain? And why is it that antipsychotic medication has no effect at all on some people?

Professor Shitij Kapur, a psychiatrist and neuroscientist and Dean at the Institute of Psychiatry, (IoP) is working with volunteer patients and brain scans to try to find some of the answers to the many hows, wheres and whys about antipsychotic medication. It's a continuation of work previously carried out when he was Chief of Research at the Centre for Addiction and Mental Health in Toronto, Canada, looking at the role of brain receptors and neurotransmitters like dopamine, and how these are affected by the drugs. He and his team have shown that most antipsychotics, both old and new, block dopamine D2 receptors, one type of the group of receptors involved in the transmission of the chemical around the brain, but to different degrees in different patients.

D2 receptors are used in different pathways in different parts of the brain for different functions. 'One of the questions we want to answer is which D2 receptors, in which regions of the brain, are the most critical for ameliorating the symptoms of psychosis,' said Professor Kapur.

Interfering with dopamine transmission in some areas of the brain can help to alleviate the symptoms, but blocking the transmission in other pathways can result in side effects.

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Blocking D2 receptors in areas of the brain involved in motor movement, for example, can lead to tremors and involuntary muscle movements. Professor Kapur and his team's research has shown that some drugs also block D3 receptors, but never D1 and D4. What effect then does that action have on the symptoms of psychosis, and what unwanted symptoms does it cause?

'We also need to find out the amount of medication we need to use,' he said. 'We have already observed that if you block 65 per cent of the dopamine system, people get relief from hallucinations and delusions. But if 80 per cent or more of the system is blocked, people get stiffness or tremors. They also report a subjective dysphoria – they say they feel like a "zombie". So while the existing drugs can improve the symptoms of psychosis, if too many receptors are blocked, it seems the more negative side effects a patient has. This has important implications for the prescribed dosage.'

Another finding emerging from this work has challenged the perceived wisdom that antipsychotic medication doesn't start working for up to three weeks. With the help of scores of patients and the insight given by brain scans, Professor Kapur and his colleagues found that the drugs have a chemical effect on the brain on the first day of taking them.

The brain imaging technique he uses is positron emission tomography (PET) and the ongoing IoP-based research is being carried out in collaboration with the PET Imaging Centre at St Thomas' Hospital on the South Bank in London. The Centre is part of both Guy's and St Thomas' NHS Foundation Trust and King's College London's School of Medicine, a sister School of the IoP.

PET scans illustrate the chemistry of our bodies, and can be designed to highlight one of the thousands of different neurotransmitters in the brain, and show its activity at any one time.

The scan involves the injection of a very small amount of a radioactive tracer designed to search and lock on to a specific chemical like dopamine. The scanner has cameras that detect the rays emitted from the radiotracers and turn them into electrical signals that are processed by a computer to generate images of different 'slices' of the brain. The greater the concentration of the chemical, the greater a signal it gives.

'We scan patients before they take the medication, and then again afterwards to measure the chemical effects in their brain of different dosages, different drugs and after different periods of time,' said Professor Kapur. 'At the same time, we keep records of their symptoms to find out whether the medication is making a difference, who gets better and who gets side effects. We can then correlate this information to what is happening inside the brain.'

Listening to patients is as important as the metabolic information gleaned from the PET scans, he said. Their personal experiences are crucial to the research. Through this process the research team has learned that the medications don't simply eradicate the delusions and the hallucinations – they often help patients to detach themselves from the symptoms, to push them 'to the back of their minds'.

'All the research is about yielding information that allows us to refine the drugs, to allow better use of the medications currently available, and ultimately to design a totally new, more effective set of medications,' said Professor Kapur.

In the long term, then, increased knowledge about the neurochemical processes involved could lead to the development of more specifically targeted drugs that do the job they are designed to do, and that job only.

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It may be that a new, third generation of antipsychotic medication will be designed to affect only, and very accurately, the levels of very specific chemicals in just the parts of the brain that are involved in creating the symptoms of psychosis.

As well as bringing direct benefits to patients, understanding how antipsychotic drugs work also gives greater knowledge about the chemical machinations of the brain that cause the symptoms of psychosis, helping to add more pieces to the jigsaw puzzle of how and why schizophrenia develops.

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