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Drugs, Behaviour and the Brain Chemistry*

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For the first time in history, we can examine exactly how drugs affect our brain, and begin to close the circle between brain chemistry and behaviour. Perhaps one day, we will be able to learn how to alter the chemistry of our own brain to decrease our reliance on drugs and make more effective use of drugs when they are needed.

Few people ever think about the chemical reactions constantly taking place inside their brains, affecting how they think, feel and act, in determining whether they are afraid, anxious or even destructive. With radioactive tracers and modern brain imaging techniques, namely, positron emission tomography (PET) and single photon emission computed tomography (SPECT), it is now possible to examine these chemical reactions within the living human brain.

Drugs affect the hundreds of billions of molecules that make up our brains, our 'universe within'. Molecules serve as chemical 'messengers' which circulate through the body until they encounter other molecules on the surface of the cells which fit their specific configuration. The molecules carrying information are called 'neurotransmitters'. They react with other molecules called 'neuroreceptors', which modify the response to the information in the neurotransmitters by interacting the way a key fits into a lock. Thus, information is passed from cell to cell. Molecular 'recognition sites' integrate the individual cells of the body, and together they make the person a unique individual.

Drugs alter the naturally-occurring chemical reactions within our brains, and affect how we think, feel and act, even to the point of inducing unconsciousness,

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making us totally unaware of our surroundings. Naturally-occurring chemicals in the brain affect consciousness and mental functioning. These chemicals affect selective neurons or large groups of neurons of the brain, just as the pedals on a piano modulate some or all of the keys.

For most of the past century, neuroscientists have explored the electrical activity of the brain by direct recording of 'action potentials' in different regions of the brains of animals, or by the clinical technique called electroencephalography (EEG).

At the turn of the century, Paul Ehrlich proposed that the pharmacological response to drugs might be due to the drug's binding to a specific chemical on the surface of the cells. The response to narcotics, such as opium, was an example, but it was not until 1973 that there was adequate proof of the existence of opiate receptors in the mammalian brain. The development of a radioactive drug, naloxone, which blocks the pharmacological action of opiates, made it possible to prove their existence. The binding of radioactive naloxone in the brain of autopsied rats proved the existence of opiate receptors, and special 'autoradiographic' pictures of the distribution of radioactivity showed that they were located along pain and respiratory neuronal pathways accounting for the pharmacological effects of naloxone. Opiate receptors were highly concentrated in the respiratory centre (opiates suppress respiration) and the medial thalamus, through which pain fibres pass.

The finding of opiate receptors in rat brain led to the search for endogenous (naturally-occurring) brain substances with opiate-like properties. It was postulated that if receptors were there, they must be binding a natural substance, not just narcotic drugs. Two such substances found were subsequently called 'endorphin' and 'enkephalin'. Since then, well over one hundred different types or subtypes of neuroreceptors have been discovered.

Most drugs act by stimulating of blocking receptors. For example, drugs that block *dopamine* receptors of a certain type diminish delusions and hallucinations in patients with schizophrenia or other psychoses, and improve abnormal thought processes. Other drugs that block receptors are: cimetidine, which blocks *histamine* receptors; and propranolol, which blocks *beta adrenergic* receptors. The widely used drug valium, with sales in hundreds of millions of dollars per year, stimulates *benzodiazepine* receptors, producing an inhibitory effect on neurotransmission, which accounts for its tranquilising effects. Receptors not only can vary in number in different parts of the brain and in different persons, but can alter their molecular structure, switching from having an excitatory to an inhibitory effect on neuronal function.

To study receptors in the living human brain, a drug called n-methyl spiperone (NMSP) which binds to dopamine receptors was labelled with the radioactive atom, carbon-11. The first successful imaging of neuroreceptors in the brain of a living human being was carried out by PET, on May 25. It showed that most of the dopamine receptors of the D2 type were found in the caudate nucleus and putamen, parts of the brain concerned with the control of movement and emotions.

The great sensitivity with which radioactivity can be measured makes it possible to measure receptor concentrations in different parts of the brain despite their extremely low concentrations, in the range of picomoles per gram. Among the first discoveries with PET was that dopamine receptors decrease dramatically in normal persons between the ages of 19 and 73 years, with most of the decrease occurring before the age of 40.

One year after the first imaging of dopamine receptors, opiate receptors were imaged in the living human brain with radioactive carbon-11 carfentanil, a drug that stimulates opiate receptors. With PET, it was possible to measure the blocking effect of drugs, such as naloxone and naltrexone, used in the treatment of drug addicts. They belong to the class of drugs, called 'antagonists'. Such drugs bind to receptors without inducing the biochemical and behavioural effects normally produced by narcotics, but they prevent subsequent binding to the receptor of the stimulating 'agonist' drugs.

PET and SPECT make it possible to examine the rates of physiological and biochemical processes in the brain of living human beings. Both methods are used in the care of patients as well as in biomedical research. PET studies require a cyclotron to produce radioactive fluorine-18 (half-life 110 minutes) and carbon-11 (half-life 20 minutes). SPECT is based on the use of longer lived radiotracers, chiefly iodine-123 and technetium-99m.

PET and SPECT depend on the use of radioactive tracers injected into the patient's vein. Some of them reflect blood flow and others take part in biochemical processes within the brain. For example, the supply of energy to the brain can be measured by injecting radioactive glucose or a related molecule, deoxyglucose labelled with radioactive fluorine-18. Such studies were conducted on experimental animals by Louis Sokoloff and his colleagues at the National Institute of Health, and were extended to living human beings in the 1970's. Measurement of glucose metabolism in the brain is now used to represent regional brain neuronal activity averaged over the 20 minutes period after administration of radiolabelled 2-deoxy-D-glucose (2-DG). With oxygen-15 labelled water, it is possible to obtain multiple images of regional brain blood flow because of the rapid rate of radioactive decay of oxygen-15 (half-life 2.07 minutes). The rate of radioactive decay of carbon-11 (half-life 20.4 minutes) and fluorine-18 (half-life 109.7 minutes) limit the number of studies that can be performed on the same persons in the same day.

Both PET and SPECT are used in the case of patients, for example, in the differentiation of depression from Alzheimer's disease as a cause of forgetfulness. Both PET and SPECT can reveal decreased glucose metabolism or blood flow in the temporal, frontal, and parietal regions if the patient suffers from Alzheimer's disease. Depression is not associated with such abnormalities, although the frontal lobes may be abnormal. Unlike the anatomically oriented imaging methods, magnetic resonance imaging (MRI) or CT, PET and SPECT provide functional or biochemical information.

Perhaps the most important immediate use of nuclear medicine technology—in the care of patients with neuropsychiatric disorders—is in the selection and monitoring of drug treatment. One of the biggest problems is the relatively high incidence of serious side effects, often leading the patients to stop taking the drug. Failure of compliance has been a major complication of the release of patients on drugs from mental hospitals. The patients are not properly supervised and often discontinue the drugs because of the side effects.

Among the first things that were discovered by PET in the 1970's was the increased regional neuronal activity stimulated in human beings or experimental animals by sound, light or touch is accompanied by increased regional blood flow or increased glucose or oxygen metabolism in the involved parts of the brain. Biochemistry revolutionised medicine at the end of World War II, based on the availability of two radioactive tracers, carbon-14 and tritium which form the basis of most of the biological research. They provide the means of defining disease at the molecular rather than the cellular level, the latter being the focus of pathology. Diseases begin to be defined as having abnormally fast biochemical processes, as for example, overactivity of the thyroid gland or decreased rates of metabolic processess, as in hypothyroidism. It is not too far-fetched to believe that some patients with mental symptoms should be classified as having 'excessive dopaminergic reactions' or other biochemical changes within certain parts of their brain. In theory, whenever a chemical process can be examined anywhere in the body, including the brain, there are at least two possible diseases, one in which the process is abnormally slow, another where the process is abnormally fast.

PET can examine the chemistry of cortical as well as subcortical structures during unconscious (sleep, anesthesia, and coma), subconscious and conscious, purposeful mental activity. The less conscious the action, the more instinctual the behaviour. For example, athletic performance is strongly influenced by subconscious brain activity. Many athletes describe a state that they call 'being in the zone', a mental state in which they have the feeling of a slowing down of time, great self-confidence and a sense that they are capable of great performance. Their brain seems to be functioning at a maximum of alertness, but without any anxiety. The phenomenon seems to occur after long hours of practice to a point where the performance is automatic. Such occassions are not common, even in athletes. Even anticipation of movement or imagination of scenes have been found to activate regions of the brain, such as the frontal lobes.

Difference in regional brain blood flow and glucose utilisation have been found in patients with schizophrenia, both during 'resting' conditions and during the performance of various mental tasks. In the early 1970's, Ingvar and Franzen observed that blood flow to the frontal cortex was lower in patients with schizophrenia than in normal persons during the performance of mental tasks. Others have found overactivity of the left cerebral hemisphere during spatio-temporal tasks in schizophrenic patients compared to normal persons in whom the task activates the right cerebral hemisphere.

Dopamine receptors of the D2 type are elevated in other types of mental illness than schizophrenia. Some patients with psychotic depression, who have delusions, hallucinations and thought disorder, but classifiable as suffering from depression rather than schizophrenia using standardised criteria, have been found to have elevated D2 dopamine receptor densities.

Patients suffering from mood disorders, such as depression or mania, following a stroke may also lead to abnormalities in certain neuroreceptor levels in some parts of the brain. Between 30 and 50 per cent of patients who have had a stroke suffer from persistent depression not related to the degree of physical impairment caused by the stroke, but related to involvement of the left cerebral hemisphere. The presence of mood disorders is related to the region damaged by the stroke. The left frontal lobe was related to depression; the right frontal lobe to manic behaviour.

PET and SPECT provide a new way to obtain objective biological markers in mental disorders. Just as it is difficult to conceive of anemia without blood counts, or hypertension without blood pressure cuff, it may some day be impossible to think of mental diseases without biochemical markers.