

Psychedelic Breakthroughs in Neuroscience: How Psychedelic Drugs Influenced the Growth and Development of Psychopharmacology

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IN THE MID-20TH CENTURY, the prevailing views in psychology and psychiatry were that mood, desires, feelings, memories, behaviors, and personalities were determined by environmental histories, childhood experiences, the interplay among reward, punishment, repression, and reinforcement, the unconscious mind, and psychosexual mechanisms, among others. Brain activity was believed to be essentially electrical in nature. Before the 1940s and early 1950s, the notion that consciousness was influenced, if not determined, by the actions of chemicals produced in the brain, was completely foreign. Important events that transformed the existing paradigms and birthed the fields of neurochemistry and neuropharmacology, leading directly to the development of psychopharmacology as a scientific discipline, are in fact centered around the discovery and investigation of the psychoactive effects of lysergic acid diethylamide (LSD), *N,N*-dimethyltryptamine (DMT), psilocybin, and other psychedelic substances.

One of the most important discoveries springing from psychedelic drug research was the elucidation of the role of serotonin in mental processes. Serotonin, whose chemical structure was determined in 1949 (Rapport, 1949), was known to be present in clotted blood since the late 1800s (Ludwig and Schmidt, 1868). Here, it has a hemostatic role: It helps prevent bleeding when tissues are damaged. Upon injury, serotonin is released from blood platelets, producing local vasoconstriction and stimulating further platelet aggregation, helping to form a clot and stanch bleeding. The discovery of serotonin in brain tissues in the early 1950s then hinted a potential role for serotonin in brain function and consciousness. The discovery of serotonin in the brain was made independently and simultaneously by a team in the United States (Betty M. Twarog and Irvine H. Page) and another team in Edinburgh, Scotland, led by Sir John H. Gaddum (Twarog and Page, 1953; Amin *et al.*, 1954). But it was Gaddum's self-experiments with LSD that were especially important in shaping early theories of the involvement of serotonin in consciousness.

Sir John H. Gaddum was a British pharmacologist who was involved in early serotonin research. On four separate occasions in 1953, Gaddum ingested LSD to learn of its effects in him (Green, 2008). Thanks, no doubt, in part to these self-experiments and in part to observations from his *in vitro* laboratory experiments with LSD and serotonin, Gaddum became the first person to propose a relationship between LSD and serotonin (Gaddum, 1953a) and to then suggest that the effects of LSD on serotonin function were responsible for LSD's psychedelic effects. His handwritten notes from a self-experiment with 86 micrograms of LSD on June 1, 1953 read as follows (Gaddum, 1953b):

9:48 My hand looks queer like a monstrous picture of a hand—that writhes about until I fix it with a look. It has interesting contrasts in its colours. I see it like an overreal picture—feel rather strange to it—as if it was someone else's [sic]. Everything in the room is rather unstable. Methedrine has not abolished the effect on sensations.

He went on to write: “The evidence for the presence of HT [serotonin] in certain parts of the brain may be used to support the theory that the mental effects of lysergic acid diethylamide are due to interference with the normal action of this HT.” (Amin *et al.*, 1954). Thus, in the person of Sir John Gaddum, there is a confluence of first-hand LSD experience and a fledgling chemical neuroscience.

Independently, D.W. Woolley and E. Shaw in New York proposed “...that the mental disturbances caused by lysergic acid diethylamide were to be attributed to an interference with the action of serotonin in the brain” (Woolley and Shaw, 1954). They further state that “Gaddum also was cognizant of the mental effects of lysergic acid diethylamide and of the occurrence of serotonin in the brain. We have surmised that he has been thinking, just as we have, about the relationship of serotonin to the mental disturbances induced by the drug.” Unlike in the case of Gaddum, however, there is no evidence that Woolley or Shaw ingested LSD themselves. Later, they wrote:

The thesis of this paper is that these pharmacological findings indicate that serotonin has an important role to play in mental processes and that the suppression of its action results in a mental disorder. In other words, it is the lack of serotonin which is the cause of the disorder. If now a deficiency of serotonin in the central nervous system were to result from metabolic rather than from pharmacologically induced disturbances, these same mental aberrations would be expected to become manifest. Perhaps such a deficiency is responsible for the natural occurrence of the diseases...In summary, the suggestions we wish to make are the following: (1) serotonin probably plays a role in maintaining normal mental processes; (2) metabolically induced deficiency of serotonin may

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contribute to the production of some mental disorders; (3) serotonin or a long-acting derivative of it may prove capable of alleviating disorders similar to schizophrenia. (Woolley and Shaw, 1954)

In these early reports, one finds the seeds of ongoing research and development of modern psychotherapeutic drugs, which has produced a multi-billion-dollar-a-year pharmaceutical industry aimed at modifying the actions of serotonin and other neurotransmitters in the brain to treat mental diseases.

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DMT has also had an important influence in the evolution of our thinking on normal and extraordinary states of consciousness. In 1961, Nobel laureate Julius Axelrod made the remarkable discovery that mammalian tissue (rabbit lung) had the ability to synthesize DMT (Axelrod, 1961). This finding was extended in the early 1970s when it was reported that biopsied human brain tissue could carry out this same biotransformation (Mandell and Morgan, 1971; Saavedra and Axelrod, 1972). The discovery that human brain tissue could produce, at least *in vitro*, small amounts of DMT, led to much speculation regarding the possible role of DMT in human consciousness. However, the analytical technology at that time was not as sensitive or robust as current methods. While some investigators were able to confirm the presence of DMT in human tissues and fluids, others failed to do so. Some scientists at the time believed that the *in vitro* observations of Axelrod and other researchers were experimental artifacts.

The issue was unresolved for almost 30 years. Then, in 1999, Michael Thompson and coworkers at the Mayo Medical School in Rochester, Minnesota, using cloning and sequencing techniques of molecular biology, discovered the human gene that codes for the enzyme (indolethylamine-*N*-methyltransfer-

ase; INMT) that synthesizes DMT from tryptamine (Thompson *et al.*, 1999). The Thompson discovery renewed discussion in, and significantly strengthened hypotheses about, a role for endogenous DMT in states of consciousness such as spiritual exaltation, dreams, creativity, near-death experiences, and other possible physiological roles. The view that the presence of DMT in mammalian tissues is only an artifact now seems untenable.

More recently, our group at the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin, using immunohistochemical techniques, has extended the original work of Thompson *et al.* by identifying the INMT protein itself in several primate central nervous system tissues (Cozzi *et al.*, 2011; Mavlyutov *et al.*, 2012). To couple the presence of the INMT protein in brain tissues with the biosynthesis of DMT within these tissues, in real-time, remains a challenging research objective. For interested readers, a critical review of the scientific literature of the past 55 years regarding the presence of DMT and other tryptamines in human tissues and fluids was recently published by Steven Barker, Ethan McIlhenny, and Rick Strassman (Barker *et al.*, 2012).

Since the time of Gaddum, research into psychedelics, serotonin, and other neurotransmitters and receptors has continued apace. Building upon the early theories of Gaddum, Wooley, and Shaw regarding the role of serotonin in the pharmacology of LSD, in the 1980s Richard Glennon and colleagues at the Medical College of Virginia at Virginia Commonwealth University were the first to name the serotonin 2 receptor (now called the 5-HT_{2A} receptor) as a major binding target for lysergamide, phenylalkylamine, and indolealkylamine psychedelic agents (Glennon *et al.*, 1984; Lyon *et al.*, 1988; Titeler *et al.*, 1988). Over the following two decades, additional binding sites have been discovered and now 40 or more additional psychedelic drug receptor sites have been identified (Ray, 2010). While the 5-HT_{2A} receptor is still widely considered to be a common receptor for psychedelic drug action, it is increasingly becoming recognized that activity at this receptor alone is not sufficient to explain the effects of psychedelic drugs. For example, other serotonin receptors, at least, have been implicated in the behavioral effects produced by indolealkylamine psychedelics in animals (Halberstadt and Geyer, 2011). There is also evidence for the direct or indirect involvement of dopamine, glutamate, norepinephrine, gamma-aminobutyric acid, and other neurotransmitters and their receptors in the actions of these drugs. The 5-HT_{2A} receptor may therefore serve as a “gateway” receptor, activation of which is necessary, but not sufficient, for psychedelic drug activity.

Apparently, the simultaneous actions of psychedelic drugs on many or all of the 40+ currently identified receptor sites,

with each psychedelic agent having a unique receptor binding and activation profile (a pharmacological “fingerprint”), shapes the variety of subjective experiences produced by these substances. Thus, although the term “psychedelic” is often used as a simplifying term, psychedelic drugs, while producing some *similar* subjective effects in humans, do not produce *identical* subjective effects, as people who have ingested these agents will readily testify. LSD is experienced differently from mescaline, which is different from DMT, which is different from TMA-2, which is different from psilocybin, which is different from 2C-B, etc. In fact, while *in vitro* data and animal behavioral models are commonly used to study these materials, these approaches are limited in that they tend to blur the qualitative, experiential differences among psychedelic drugs, differences which human beings can easily distinguish. *In vitro* and animal data can supplement, but in no way substitute for, human experience, which of course is the *sine qua non* of psychedelic drug effects.

The problem of choosing uniform criteria to define psychedelic drugs and the experiences they produce is certainly not new. One approach put forth in the 1970s was to define psychedelic drugs to the extent that they mimic the effects of LSD. Although this definition is rather circular, it does put the psychedelic experience itself squarely at the center of the discussion. According to Lester Grinspoon and James Bakalar, “Whether a drug should be regarded as psychedelic or not can be said to depend on how closely and in what ways it resembles LSD; the resemblance must be judged by the drug’s cultural role as well as by its range of psychopharmacological effects. From this point of view, the group of psychedelic drugs has a clearly defined center and a vague periphery...” (Grinspoon and Bakalar, 1979). Linking molecular binding events to animal behavior to human experiences remains a tantalizing but incompletely realized goal.

It is apparent from the literature reviewed above and other sources that much present-day research into neurotransmitters and drugs that affect their function in the brain is directly traceable to the experiments and writings of scientists investigating the mechanisms of action of LSD, DMT, and other psychedelic compounds.

(For a superb historical treatment of this research, told in autobiographical form by a veritable Who’s Who of the early psychopharmacologists themselves, see the excellent book: *The Rise of Psychopharmacology and the Story of CINP, As Told in Autobiography, Volume 1*; TA Ban, D Healy, E Shorter, eds., published by CINP Central Office, Scotland, UK (1998), ISBN 963-408-105-3; cinp.org.)

In light of these discoveries in neurochemistry, the suppositions of psychology and psychiatry with respect to the

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origin and nature of consciousness and psychological diseases were required to undergo significant revision. It became necessary for psychology and psychiatry to incorporate observations from neurobiology into models of mental functioning. Neurochemistry and neuropharmacology began to assume dominant roles in consciousness research and in the medical treatment of mental illness by the late 1950s and into the 1960s. In particular, it became obligatory for psychotherapeutic practices to employ psychoactive drug treatments, which were rationally derived from the experimental discoveries of neuropharmacology, as a major approach to psychological healing. Although there remains much that could be improved, the effectiveness of these drugs has undoubtedly benefited countless lives.

Interest in neurotransmitters and drugs that modulate their activity continues to motivate much current research in academia, the pharmaceutical and biotechnology industries, and government institutes. For a person seriously interested in such research—especially if it involves psychedelic drugs—Ph.D. or M.D. level academic study or clinical training, at least, is usually necessary. Several years of post-doctoral training may eventually lead to a role as a principal investigator directing basic science research or as a clinical study director supervising human studies. In any case, post-baccalaureate graduate study at any level will lead to more opportunities to be involved, perhaps as a team member, in doing research at a university, a pharmaceutical company, the National Institutes of Health, or a private research foundation. The long line of consciousness researchers seeking to develop tools to study the mind and improve mental health awaits you as a participant! 🍀

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