The discovery of GABA in the brain

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Martin J. Spiering [1]

Some scientific discoveries land with a boom only to fizzle out and become a small blip—but there are times when this order is reversed. Such was the case with the discovery of γ-aminobutyric acid (GABA) in the brain, reported in 1950. In a study published in the *Journal of Biological Chemistry* (1), preceded by a brief conference report shortly before that (2), Eugene Roberts (Fig. 1) and Sam Frankel not only identified GABA as a major amine in the brain, but also reported that it is produced and preferentially accumulates in this organ.

Somewhat surprisingly, the initial response to this discovery was rather muted. In the first 5 years following Roberts and Frankel's report, which was accompanied by two other articles on GABA in the brain published in the same JBC issue (3, 4), according to PubMed, only four additional studies of GABA in the brain were published at that time.

Whether the research community was stunned into awed silence or hushed disbelief or whether this lackluster reaction simply reflected a lack of methods to quickly test GABA's function is difficult to tell as we approach the 70-year mark of this finding. But, we do know that at first no one seemed to have an inkling as to what GABA might be doing in the brain.

GABA's activity in the brain was eventually clarified in 1957 when researchers in Canada reported that an unknown compound having inhibitory activity on crayfish neurons was in fact GABA (5). "The GABA receptors mostly have an inhibitory input, and they are the major inhibitory receptors in the brain," says Baruch Kanner of Hebrew University Hadassah Medical School in Israel and member of the JBC Editorial Board who studies GABA transporters. With that hindsight, it is now clear that Roberts and Frankel's discovery marked a major milestone in the quest for unraveling how neurotransmitters control brain activity.

The story of GABA and Roberts' research career in many ways exemplify how discoveries and careers are often molded from humble and sometimes obscure beginnings. Roberts' personal history as a first-generation immigrant mirrors that of legions of researchers working in the United States. Born Evgeny Rabinowitch in 1920 in southern Russia, Roberts arrived in the U.S. in 1922, settling with his parents in Detroit, Michigan. Awarded a scholarship from Wayne State University when he was only 16, Roberts graduated with a B.S. (magna cum laude) in chemistry in 1940. He then went on to study biochemistry, earning an M.S. in 1941 and a Ph.D. in 1943 from the University of Michigan in Ann Arbor.

After a short stint as an assistant head of the Manhattan Project's inhalation section at the University of Rochester, New York, working on the toxicology of uranium dusts, Roberts moved to Washington University in St. Louis, Missouri, in 1946. There, he became interested in amino acids in the brain, studying them in normal and neoplastic brain tissues.

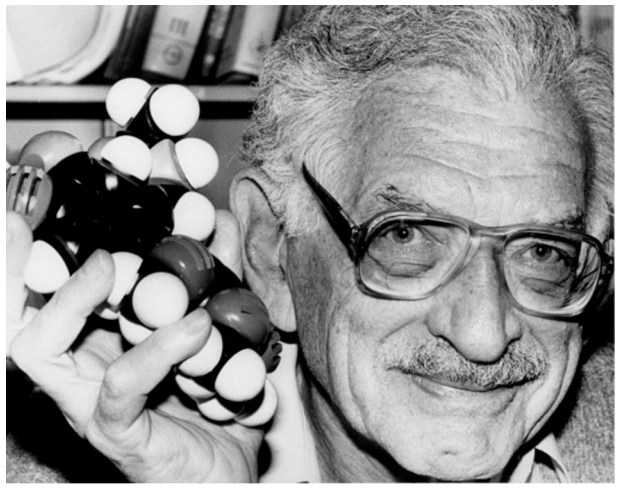

Figure 1. Eugene Roberts, who first reported that GABA is a major amino compound in the brain. Photo from Scholarpedia, used under Creative Commons.

This was at a time when *metabolomics* or *proteomics* would have been considered bizarre futuristic terms, when even mass spectrometry or other tools now considered standard in analytical chemistry were far off on the horizon or too laborious and time-intensive for the task at hand. Instead, Roberts used paper chromatography, and a chemical dye, ninhydrin, that reacts with and stains primary amines, to isolate and identify free amino acids in mouse brain extracts.

As he meticulously analyzed these extracts, Roberts came across a ninhydrin-reactive compound whose migration on paper chromatograms did not match any known amine-containing compounds. What's more, this mysterious amino acid–like metabolite apparently accumulated at much higher levels in the brain than in other tissues. Acid treatments of brain tissues didn't increase these levels, suggesting that this amine exclusively occurs in the free form in the brain. Luckily, it was a lone wanderer, migrating far enough from other ninhydrin-staining compounds, enabling Roberts and Frankel to extract it from strips cut from the chromatograms.

The researchers ran the strip-extracted compound along with carefully prepared reference standards in different solvent systems. A technique developed by a colleague at Washington University, Sidney Udenfriend, called the *isotope derivative method* (published in the same JBC issue (4)) also helped them to home in on the unknown amine. Through this multipronged approach, Roberts and Frankel concluded that this brain-associated amine was GABA. Taking it a step further, using radioactive labeling of potential GABA precursors, the research duo also demonstrated that brain tissues can convert another common cerebral amino acid, glutamic acid, to GABA (1).

Lila Gierasch at the University of Massachusetts, Amherst, nominated this paper as a Classic.

[1] Martin Spiering is the technical editor at JBC. E-mail: mspiering@asbmb.org.

The 1957 finding revealing that GABA inhibits the firing of action potentials in neurons presented another novelty. Other amine-containing neurotransmitters whose activities were known at the time, such as norepinephrine and acetylcholine, are activating (excitatory) ones. Kanner notes that the amino acid glycine also can inhibit brain neurotransmission, but "GABA is clearly the most abundant one."

Accordingly, researchers are interested in targeting the GABA system to manage epilepsy, which arises from overexcitation of the brain's neurons. An initially promising avenue has been to prevent or slow reuptake of GABA once it is released into synapses by targeting its transporter, a strategy that has been successful for several other brain neurotransmitters to manage some other disorders.

"By inhibiting the GABA transporter, GABA is staying around [at the synapse] for a longer time. Then you get more inhibition and that could be potentially an anti-epileptic drug because the inhibitory input becomes bigger," says Kanner. However, although showing initial promise, compounds that prevent GABA reuptake or else stimulate its receptor have not yet made it beyond clinical trials, probably because of side effects, Kanner says.

These snags notwithstanding, GABA's discovery has spurred many research activities; as of this writing, a search of PubMed for "gamma-aminobutyric acid" and "brain" returns about 30,000 papers on the topic.

These efforts include those of Kanner, who is studying the mechanism by which the GABA transporter operates. Kanner says he recalls meeting Roberts some 40 years ago and talking with him about his own research plans and findings on GABA. "I think it must have been quite gratifying for him to see how [important] this molecule that he discovered in the brain is and how all the aspects of its action are being investigated," Kanner says. "I think it's wonderful that his central contribution will be remembered."

Roberts died in 2016 and would have turned 100 in 2020.

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