The Cocaine Receptor. Reminiscences 5

Drugs, including cocaine, work by binding to some specific site referred to as its receptor. Binding to the receptor is needed to produce its effects. The brain can be loaded with the drug, but if it does not get to the receptor, there will be no effect.

A critical question was "What is the receptor for the addicting properties of cocaine?" Cocaine has many effects, but the question is only about the addicting properties of the drug. This question was the focus of our research in the mid-1980s. At that time, the cocaine/crack epidemic was raging, and the question was of fundamental importance in public health research. It might lead to new medicines for treating drug addicts.

Let me restate the problem. In say 1985, when we started on the problem, cocaine was known to act at or bind to several sites in brain tissue. These sites included the serotonin transporter, the norepinephrine transporter, and the dopamine transporter. It also bound to sodium channels but in a minor way. So, the question came down to which of the three transporters was the cocaine binding site that produced cocaine addiction. Other sites produced the other effects of cocaine.

Our approach was to test a variety of cocaine analogues at the three transporters (and other sites), and then compare that data to the ability of the analogues to produce addiction. Roughly speaking, the goal was to find the transporter where weakly binding analogues would be weak in producing addiction, and where potent binding analogues would be potent in producing addiction. If such a correlation could be found for one of the transporters, then that would be the cocaine "receptor" or binding site related to addiction.

So, we had our strategy, and now I needed to pull a research team together. Mary Ritz was a new post-doctoral fellow in the lab and she would be responsible for carrying out the experiments; she would be the main researcher responsible for the project. In retrospect, she did the best possible job. Next, I need someone expert in the behavior of addiction and assessing addiction. I asked Steve Goldberg who was on the other side of the building to work with us. I explained to him that I knew he knew nothing about this kind of work, and he would not have to do many or perhaps any experiments, but we hoped for his advice and thoughts. Steve agreed and he recruited one of his people, Rick Lamb, to be part of the project as well. Our basic team was set.

We needed an animal model of addiction, and we selected the self-administering monkey. Several people suggested this, including Marion Fischman, Joe Brady, and Bob Schuster. If a drug was self-administered, then it had an addiction liability. Some drugs were more potent than others, i.e., the drugs were self-administered at lower concentrations than other less potent drugs. Then we collected data on the self-administration of a series of large cocaine-like compounds called phenyl tropanes as well as on some additional large compounds that were not transported; they just blocked the transporters like cocaine. We further studied

the compounds for which we had self-administration data in binding assays where we determined the relative binding affinity of the compounds at the three transporters. Binding was an approach that looked at the actual physical interaction between the chemical, such as cocaine, and the receptor.

Once we had the data for at least 10 reasonable compounds, we compared their potency in self-administration with their potency in binding to the three transporters. This took considerable work, with many ideas being tested. Mary Ritz did an outstanding job handling all this work.

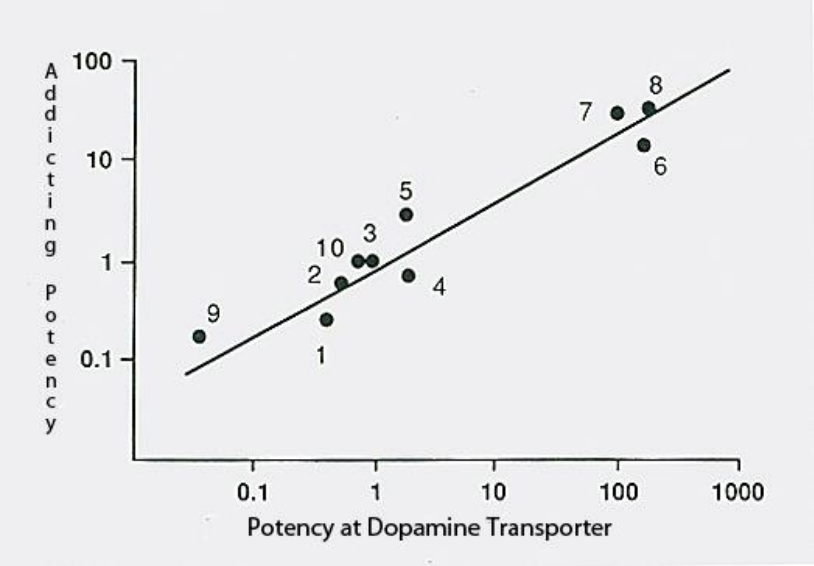
The result was worth it. We were excited. The addiction liability closely correlated with binding to the dopamine transporter ($P<0.001$) and not the others ($P<0.45$, $P<0.93$). Some critics felt that not all of the 10 compounds were acceptable for use, so we redid the analysis leaving out the contested ones. While the P values changed, the selectivity for dopamine did not. The results were astonishingly clear. While cocaine bound to many sites in the brain, it was the binding to the dopamine transporter that was related to the self administration of drugs and addiction.

It turned out that there were existing behavioral pharmacology papers that indeed suggested that the DAT was the site for cocaine addiction. This was nice work that we were not really aware of. Our work supported those papers and their conclusions. But the way we did our study, by direct binding, was a clearer and more direct approach than those used by the behavioral papers. Drugs can produce behaviors in a variety of ways. But this binding study showed a correlation with a direct binding to the dopamine transporter. It was a step further in specificity. Binding had only one interpretation. It meant that we were studying the direct molecular binding site of cocaine.

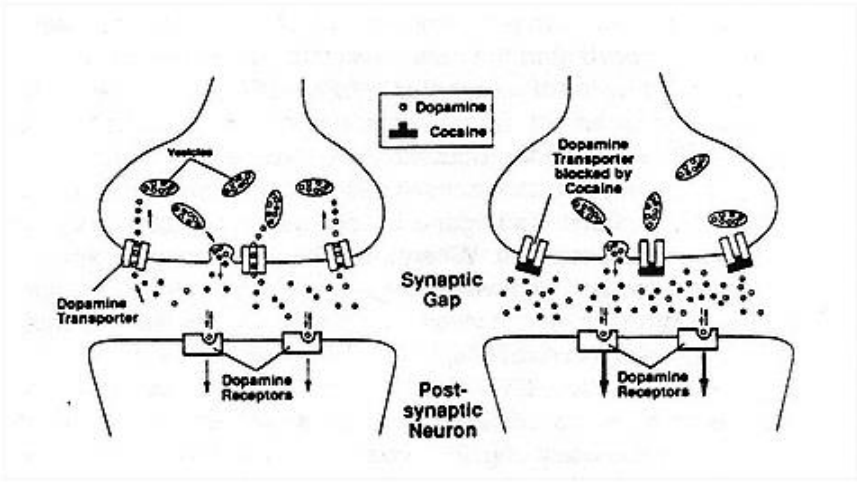
Our results were a breakthrough. They facilitated brain imaging of the cocaine receptor, it led to new behavioral studies, and stimulated the medicinal chemistry of possible medications for cocaine addicts. It produced another awareness of ways to study addiction in general, not only cocaine addiction.

Our publication in Science was of immediate interest throughout the scientific community. It is my most cited scientific publication.

I gratefully acknowledge at least a dozen colleagues who discussed our approach, supplied compounds and technical and clerical skills. I am especially grateful to the knowledgeable colleagues who helped with the statistical multiple regression analysis which was so critical. They are all named in our publication: Ritz et al., Science 1987, volume 237, pp 1219-1223.



This data is the fundamental correlation between binding at the dopamine transporter and addiction liability. Each dot represents one compound. Compounds that are weak at the transporter are weak in addiction liability, and compounds that are potent at the transporter are potent in the addiction assay. This correlation was not found for any other binding site or receptor that was examined. This figure is modified from one in the Ritz et al Science paper.



This figure depicts the generally accepted dopamine hypothesis of cocaine addiction. The functional purpose of the dopamine transporter to remove released dopamine from the synapse and terminate neurotransmission. When cocaine is present in the brain, it blocks the dopamine transporter, and then dopamine builds up in the synapse and the receptors get more stimulation. This high concentration of dopamine results in the sensations, feelings and actions that result in addiction. This figure is from Kuhar et al, Trends in Neuroscience, Vol. 14, p 299, 1991.