The Cocaine Receptor.

Drugs, including cocaine, work by first 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. The receptor is a molecule, and it is like a button on a control panel that the drug must push to produce an effect.

A critical question was "What is the receptor for the addicting properties of cocaine?"
Cocaine has many effects, but the question here is only about the addicting properties of the drug.
This question was the focus of our research in the mid1980s. At that time, the crack/cocaine epidemic was raging, and the question was of fundamental importance in public health research. Understanding the receptor could lead to new medicines for treating drug addicts.

Let me restate the problem. In about 1985 when we started on the problem, cocaine was known to act at or bind to several different sites in the brain. 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 such as increasing blood pressure, sleep effects and local anesthesia. 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.

The strategy (used before) was to find the single binding site 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. This paragraph is the key to understanding this study. This strategy was used to find many other drug receptor sites; I was a part of some of these studies and I had the relevant experience. As described below, we were successful in this effort.

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 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 in animal studies. I asked Steve Goldberg who was on the other side of the building to work with us. I explained to him that while I knew he knew nothing or little about binding, he would be asked for his thoughts. I would be in charge of the project. Steve agreed and he recruited one of his people, Rick Lamb, to be part of the project as well. Our basic team was set.

Next, 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 potent 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 blocked the transporters like cocaine.

To make a long story short, The addiction liability of cocaine and other similar compounds closely correlated with binding to the dopamine transporter ($P<0.001$) and not the other

transporters. (P<0.45, P<0.93). 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 also suggested that the dopamine transporter was the site for cocaine addiction. But the way we did our study, by direct binding, was a clearer and more direct approach than those used in 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 is between two molecules only and had only one interpretation. It meant that we were studying the direct molecular binding site of cocaine related to addiction.

Our results were a breakthrough. They facilitated brain imaging of the cocaine receptor, 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 helped us and 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.

END.

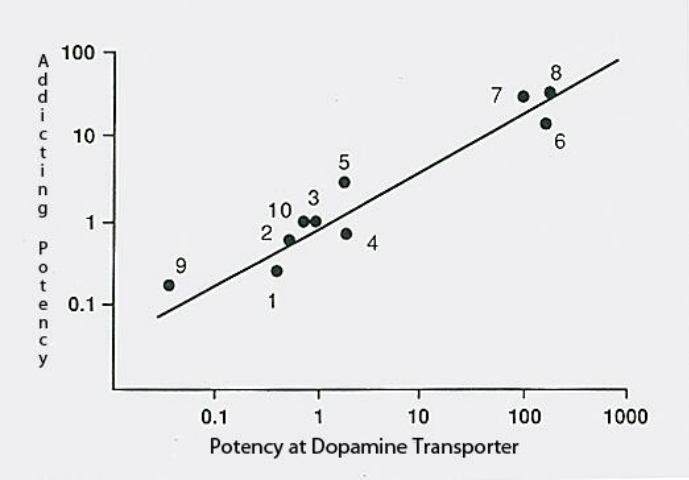

Figure 1. This data is the fundamental correlation between binding at the dopamine transporter and addiction liability. Each dot represents one compound. Compounds that are weak at the transporter are weak in addiction liability, and compounds that are potent at the transporter are potent in the addiction 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 (1987).

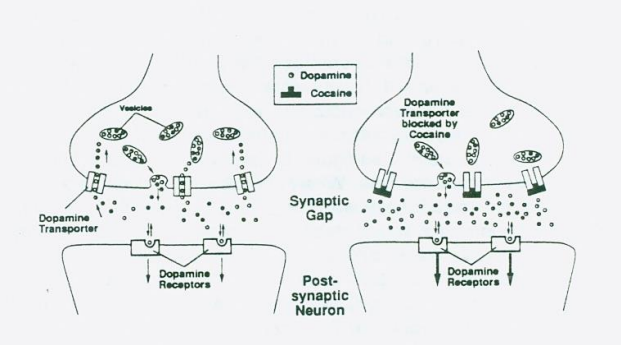

Figure 2. This figure depicts the generally accepted dopamine hypothesis of cocaine addiction. The functional purpose of the dopamine transporter is to remove released dopamine from the synapse and terminate neurotransmission. When cocaine is present in the brain, it blocks the dopamine transporter, and then dopamine builds up in the synapse and the receptors get more stimulation. This results in a high concentration of dopamine that produces the sensations, feelings and actions
that result in addiction. This figure is from Kuhar et al, Trends in Neuroscience, Vol. 14, p 299, 1991.