6. Mothers, Parkinson's, and obesity.

We carried out more studies that impact human problems. Three of these are described here.

Mothers and drugs.

When human drugs users were studied in many places, it appeared that parental drug use affected drug use in their children. My group and others decided to study this in the context of drug abuse.

We approached it by taking newborn litters of rats and stressing some litters by separating mothers from pups for some time, up to three hours. This was done only around the time of birth, for 2 weeks, and then all the litters were treated the same.

When the pups became adults, they were tested for drug intake, and amazingly the rats that had been separated from moms around birth took more drugs! **This says that stresses or negative experiences around the time of birth can change drug intake patterns in rats (and humans) for the rest of their lives!** I use exclamation points because this is striking. We still marvel at this finding. By studying these animals further, we might be able to see how the brain changes and why the rats become more interested in drugs.

There are a lot of technical details that I am skipping over in order to make a point. There were other scientists in other places involved in this work, and at Emory, Dr Paul Plotsky was expert in maternal separation and helped us carry out our work.

Three of our publications on this topic are:

Maternal separation alters drug intake patterns in adulthood in rats.
Moffett MC, Vicentic A, Kozel M, Plotsky P, Francis DD, Kuhar MJ. Biochem Pharmacol. 2007 Feb 1;73(3):321-30. doi: 10.1016/j.bcp.2006.08.003. Epub 2006 Sep 8.PMID: 16962564

Maternal separation and handling affects cocaine self-administration in both the treated pups as adults and the dams. Moffett MC, Harley J, Francis D, Sanghani SP, Davis WI, Kuhar MJ.J Pharmacol Exp Ther. 2006 Jun;317(3):1210-8. doi: 10.1124/jpet.106.101139. Epub 2006 Mar 3.PMID: 16517692

Effects of early maternal separation on ethanol intake, GABA receptors and metabolizing enzymes in adult rats. Jaworski JN, Francis DD, Brommer CL, Morgan ET, Kuhar MJ. Psychopharmacology (Berl). 2005 Aug;181(1):8-15. doi: 10.1007/s00213-005-2232-4. Epub 2005 Oct 15.PMID: 15830234

Parkinson's Disease Testing

The defect in the brain in Parkinson's Disease a loss of dopamine-containing neurons in parts of the brain. The dopamine transporter is found uniquely in these neurons. So when the neuron die and Parkinson symptoms develop there is a loss of transporters.

Because much of our work was on the development of chemicals that could be used in imaging dopamine transporters, we were able to use these chemicals along with Brain imaging to diagnose Parkinson' Disease. Images from Parkinson's patients showed no or many fewer transporters than normal. This was an excellent diagnostic procedure to identify Parkinson's Disease.

This procedure is being studied today by many. The field and our achievements owe much to my collaborator, an exceptionally talented medicinal chemist, Dr F Ivy Carrol.

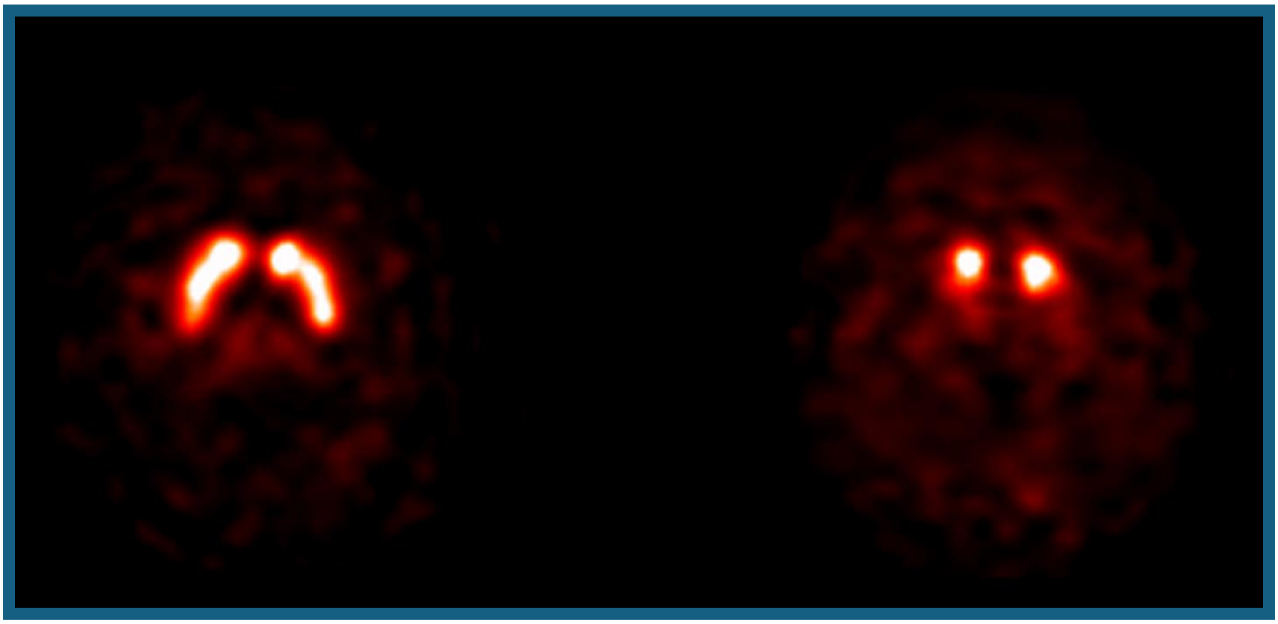

Figure. These are images of dopamine transporters in slices of brain from a normal person (left) and from a Parkinsons patient (right). The brighter the image the greater number of transporters. It is clear that the Parkinson's patient has a much less of a bright area which indicates fewer transporters and fewer dopamine neurons. This suggests that a brain imaging approach would be a good diagnostic procedure for Parkinson's.
(Spect imaging with RTI-55)

Citations:

A multicenter assessment of dopamine transporter imaging with DOPASCAN/SPECT in parkinsonism. Parkinson Study Group. [No authors listed] Neurology. 2000 Nov 28;55(10):1540-7. doi: 10.1212/wnl.55.10.1540.PMID: 11094111

High potency cocaine analogs: neurochemical, imaging, and behavioral studies.
Boja JW, Cline EJ, Carroll FI, Lewin AH, Philip A, Dannals R, Wong D, Scheffel U, Kuhar MJ.Ann N Y Acad Sci. 1992 Jun 28;654:282-91. doi: 10.1111/j.1749-6632.1992.tb25974.x.

Evaluation of [11C]RTI-121 as a selective radioligand for PET studies of the dopamine transporter.
Hume SP, Luthra SK, Brown DJ, Opacka-Juffry J, Osman S, Ashworth S, Myers R, Brady F, Carroll FI, Kuhar MJ, Brooks DJ.Nucl Med Biol. 1996 Apr;23(3):377-84. doi: 10.1016/0969-8051(96)00019-4.PMID: 8782251

CART peptide

In around 1995, before the genome was published, there was an effort to find new genes that were involved in drug addiction. One of the genes was the CART gene, which produced the CART peptide. This peptide was a chemical that acted like a neurotransmitter and neurohormone. Our group looked at the role of CART gene in the action of cocaine and feeding.

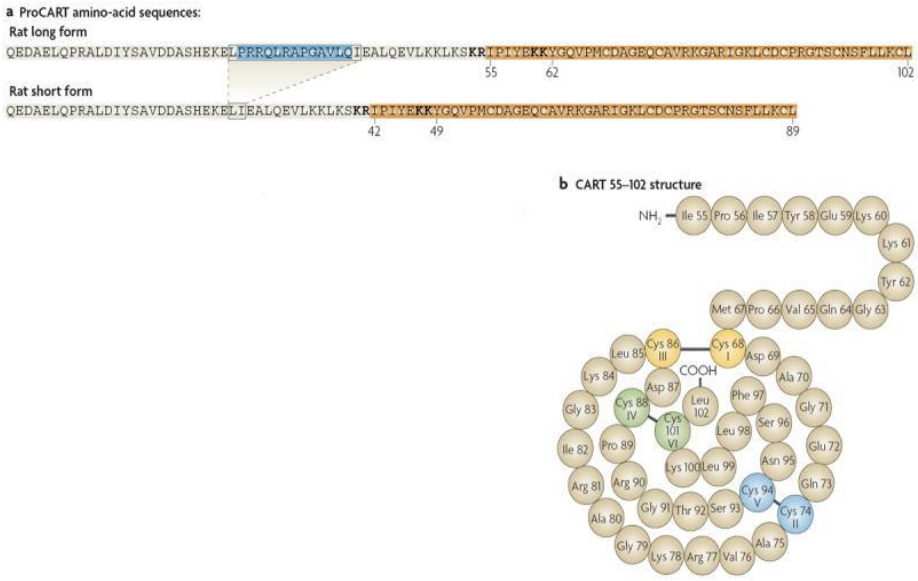

Figure showing in a) the amino acid sequence of the peptide, and in b) the folding of the peptide. (From Rogge et al cited below.)

By injecting CART into the nucleus accumbens, and then looking at the effect on the action of cocaine, we observed that CART peptide had complex effects. If cocaine had small effects, the peptide increased it, and if cocaine had big effects, the peptide reduced it. So CART peptide was a regulator and exerted an effect to keep the effects

of cocaine in a window or narrow range. This was referred to as a rate effect. It is very interesting that it works in this way.

In other experiments we found that some CART peptides had effects on feeding – it reduced feeding. Because this was an important finding, many research groups started exploring this. Then an amazing thing happened, A group in Italy found that a mutation in the CART gene resulted in obesity; this discovery in humans produced a focus on CART peptide and feeding. This is still going on today. It is hoped that understanding the role of CART in feeding will someday lead to improved medications or other treatments to control body weight.

The field of CART peptide research today is massive. If you have an interest in it, please go to the scientific literature found, perhaps, in PubMed.

Citations.

CART Peptide Regulates Psychostimulant-Induced Activity and Exhibits a Rate Dependency. Kuhar MJ, Job MO .J Drug Alcohol Res. 2017;6:236032. doi: 10.4303/jdar/236032. Epub 2017 May 26.PMID: 29225992

CART peptides: regulators of body weight, reward and other functions. Rogge G, Jones D, Hubert GW, Lin Y, Kuhar MJ. Nat Rev Neurosci. 2008 Oct;9(10):747-58. doi: 10.1038/nrn2493.PMID: 18802445