Neuropsychopharmacology (2009) 34, 1172–1173

www.neuropsychopharmacology.org

Letter to the Editor

On the Use of Protein Turnover and Half-Lives

Michael J Kuhar*[,1]

[1]*Neuroscience Division, The National Yerkes Primate Research Center, Emory University, Atlanta GA, USA*

Neuropsychopharmacology (2009) **34,** 1172–1173; doi:10.1038/npp.2008.190; published online 15 October 2008

Another excellent paper from the Porrino and Nader group has examined the recovery of the dopamine parameters (D1, D2, and DAT) after abstinence from long-term self-administration of cocaine in monkeys (Beveridge *et al*, 2008). As the authors note, this is important because of the findings in humans and other species that there are changes in brain after cocaine use, and an enduring question has been whether these changes can revert to normal, particularly in humans. This has implications for the potential degree of recovery from addiction.

This letter is not a criticism, but rather an addition to the ongoing discussion as to the meaning and possible directions for such experiments. It discusses the possible importance of some older concepts including turnover and half-lives of proteins as a reflection of the activity of a system. Turnover is the rate at which the molecules of a substance (in this case, a protein) are replaced. It is related to the synthesis and degradation rates of the substance. Half-life relates to the time it takes to replace half of the molecules. A more rigorous discussion of these topics can be found in the literature (Kuhar and Joyce, 2001; Kimmel *et al*, 2003). Two examples where these concepts are used are described below and they show how these parameters can help interpret data.

The first example focuses on the fact that this (Beveridge *et al*, 2008) and similar studies measure levels of these proteins (D1, D2, and DATs). There is good evidence that measuring levels alone does not always provide the complete picture. The turnover or half-lives of the proteins may be different even though the levels are the same. For example, the half-life of DAT in rats, measured after 10 days of passive cocaine administration followed by 10 days of withdrawal, was about halved in the striatum from cocaine-treated animals compared to saline-treated animals. But, the level or Bmax of DAT was not different in the cocaine withdrawal group compared to the saline withdrawal group, even though the half-lives were different (Kimmel *et al*, 2003). The levels of a protein might not change because the synthetic machinery can perhaps keep up with its use and degradation even though there might changes in the latter. The next question is: what is the significance of changes in turnover rates and half-lives of DAT? In one sense it implies something at the cellular level. Also, it may reflect the relative stimulation of DA receptors or other factors (Kimmel *et al*, 2001). Therefore the protein might be actively engaged at a new level even though its levels on a molar basis are not changed.

It is possible to measure the turnover and half-lives of DA receptors and DATs in animals (see Kimmel *et al*, 2001 for references). Turnover and half-life have long been considered advantageous measurements for the activity of neurotransmitter-specific neurons (Brodie *et al*, 1966; Iversen and Glowinski, 1966). In any case, a discussion of the value and significance of turnover and its associated parameters in PET measurements seems worthwhile although perhaps technically difficult.

A second example is a species-related one. Do the results in monkeys relate directly to humans in a quantitative fashion? Perhaps not. It is known that the half-life, degradation rate, and turnover of the same protein can differ among species (Kuhar and Joyce, 2001). This is relevant to the current topic because the half-life determines how quickly protein levels adjust to new levels. For example, the half-life of MAO-B in rat brain is 7–11 days, in pig brain 6.5 days, in baboon brain about 30 days, and in human brain about 40 days (Kuhar and Joyce, 2001). If the half-life in humans is different from that in monkeys, the rate of recovery of the protein levels will also be different in the two species. So, if proteins in the DA system have longer half-lives in humans than monkeys (longer half-lives equate to a longer recovery time) recovery of the dopamine system from cocaine treatment is likely to take a longer time in humans. Beveridge *et al* (2008) report that in monkeys D2 receptors in the striatum are back to normal after 30 days of withdrawal, but Volkow *et al* (1993) show that in humans there is still a reduction in D2 receptors at 100 days of withdrawal. This difference is likely, at least partly, due to the differences in half-lives in the different species. An awareness of half-lives and their significance can be useful when considering proteins in different species.

In conclusion, the half-lives of proteins may change without a change in levels, and the full significance of this remains to be determined although it may be related to the relative activity or utilization of the proteins. Also, because

*Correspondence: Professor MJ Kuhar, Neuroscience, Yerkes Resaerch Center at Emory University, 954 Gatewood Rd NE, Atlanta, GA, 30329, USA, Tel: +404 727 1737, Fax: 404 727 3278,
E-mail: mkuhar@emory.edu
Website: www.emory.edu/neuroscience/kuhar/index.html
Received 9 September 2008; accepted 18 September 2008

of species differences in half-lives for a given protein, the recovery rates of these proteins will not be the same in different species. It is possible to quantify recovery rates, half-lives, turnover times, and the degradation rate constants of many proteins in animals. Insights to the physiologic nature of these parameters are likely to deepen our understanding of cellular processes occurring during addiction and recovery. Although the full significance of the parameters is not obvious at this time, a consideration of their value seems worthwhile.

DISCLOSURE/CONFLICT OF INTEREST

Over the past 3 years, the author has received an honorarium from Cephalon and funding from Pfizer Inc.

REFERENCES

Beveridge TJ, Smith JR, Nader MA, Porrino LJ (2008). Abstinence from chronic cocaine self-administration alters striatal dopamine systems in rhesus monkeys. *Neuropsychopharmacology* (e-pub ahead of print).

Brodie BB, Costa E, Blabac A, Neff NH, Smookler HH (1966). Application of steady state kinetics to the estimation of synthesis rate and turnover time of tissue catecholamines. *JPET* **154**: 493–498.

Iversen LL, Glowinski J (1966). Regional studies of catecholamines in the rat brain. II. Rate of turnover of catecholamines in various brain regions. *J Neurochem* **13**: 671–682.

Kimmel HL, Carroll FI, Kuhar MJ (2003). Withdrawal from repeated cocaine alters dopamine transporter protein turnover in the rat striatum. *JPET* **304**: 15–21.

Kimmel HL, Carroll FI, Kuhar MJ (2001). Dopamine D1 and D2 receptors influence dopamine transporter synthesis and degradation in the rat. *JPET* **298**: 129–140.

Kuhar MJ, Joyce AR (2001). Slow onset of CNS drugs: can changes in protein concentration account for the delay? *Trends Pharmacol Sci* **22**: 450–456.

Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ *et al* (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* **14**: 169–177.