CC/NUMBER 38
SEPTEMBER 19, 1988

This Week's Citation Classic®

Kruszynski M, Lammek B, Manning M, Seto J, Haldar J & Sawyer W H. [1-(β-mercapto-β,β-cyclopentamethylenepropionic acid),2-(*O*-methyl)tyrosine]arginine-vasopressin and [1-(β-mercapto-β,β-cyclopentamethylenepropionic acid)]arginine-vasopressin, two highly potent antagonists of the vasopressor response to arginine-vasopressin. *J. Med. Chem.* 23:364-8, 1980.
[Dept. Biochemistry, Medical Coll. Ohio, Toledo, OH and Dept. Pharmacology, Coll. Physicians & Surgeons, Columbia Univ., New York, NY]

This paper describes the synthesis and some pharmacological properties of two arginine-vasopressin (AVP) analogs that exhibit unexpectedly potent and selective vasopressin V_1 (vasopressor) antagonism. One of these, [1-(β-mercapto-β,β-cyclopentamethylenepropionic acid),2-(*O*-methyl)tyrosine]AVP ($d(CH_2)_5Tyr(Me)AVP$), has been widely used experimentally for probing the functions of endogenous AVP in normal and pathophysiological states. [The *SCI*® indicates that this paper has been cited in over 250 publications.]

Maurice Manning
Department of Biochemistry
Medical College of Ohio
Toledo, OH 43699
and
Wilbur H. Sawyer
Department of Pharmacology
College of Physicians & Surgeons
Columbia University
New York, NY 10032

March 17, 1988

The high potencies of the V_1 antagonists described in this paper came as a delightful surprise. They had been synthesized by Marian Kruszynski and Bernard Lammek, visiting investigators from the University of Gdansk, Poland, working with Maurice Manning (a native of Ireland) at the Medical College of Ohio. They were characterized pharmacologically in W.H. Sawyer's laboratory at Columbia University.

At that time we were trying to design antagonists of the antidiuretic (V_2) responses to arginine-vasopressin (AVP). Despite almost 25 years of intensive efforts by many laboratories, this remained an elusive goal. In our search for V_2 antagonists we employed structural modifications that had led the laboratories of V. du Vigneaud and J. Rudinger to promising oxytocin antagonists.[1,2] These included the $d(CH_2)_5$ and Tyr(Me) substitutions at positions one and two, respectively. When these substitutions were combined in AVP itself, we were greatly surprised to find that the resulting peptide, $d(CH_2)_5Tyr(Me)AVP$, was almost five times as potent as any V_1 antagonist we had seen before and was much less active as an antidiuretic agonist. Based on the properties of structurally related molecules, we had expected a much less potent antagonist.

These findings were significant for three reasons: (1) This paper elicited an extraordinary number of requests for samples of $d(CH_2)_5Tyr(Me)AVP$ from scientists throughout the world. Consequently, this antagonist has played a key role in hundreds of studies on the putative physiological functions of AVP. We are thus not surprised that this publication has received so many citations. Indeed, if properly cited, the number would be much larger. In some instances no citation is given, while in many others the paper cited is one of our reviews. Nevertheless, we are delighted that this compound has turned out to be useful to so many other scientists. It still remains one of the most often requested analogs of the many we have published. (2) Although $d(CH_2)_5Tyr(Me)AVP$ was not a V_2 antagonist, it (a) encouraged us to stay with the $d(CH_2)_5$ substitution in our further search for V_2 antagonists and (b) played a pivotal role in the realization of this goal. The long search for the first effective V_2 antagonists finally ended in 1981 with the discovery that 4-valine substituted analogs of $d(CH_2)_5Tyr(Me)AVP$ were in fact V_2 antagonists.[3] (3) These findings served to further underscore the words of du Vigneaud (with whom Manning had the privilege of working in the early 1960s): "True exploratory research is really the working out of a winding trail into the unknown."[4]

When we began this collaboration 13 years earlier in 1967, we had virtually no interest in vasopressin antagonists. Our primary objectives were focused on problems related to the evolution of the neurohypophysial peptides. With the invaluable assistance of the Merrifield solid phase method,[5] generous National Institutes of Health funding, and a large measure of serendipity, we soon began uncovering new analogs of oxytocin and vasopressin that exhibited potent and selective agonistic properties. We thus found ourselves following inevitably in the footsteps of such pioneers of structure-activity studies on neurohypophysial peptides as du Vigneaud, Rudinger, B. Berde and R.A. Boissonnas, and their coworkers[1,2] on a trail leading towards the long-sought V_2 antagonists. Along the way, as described in this *Citation Classic*, we discovered a real gem, $d(CH_2)_5Tyr(Me)AVP$. Thus, the discovery of $d(CH_2)_5Tyr(Me)AVP$ will always be very special, since it epitomizes the joy of such findings and the ripple effects they may have.

Unexpected findings continue to be a recurring motif along this trail—as evidenced by our recent exciting discovery that a ring structure is not required for V_1 or V_2 antagonism.[6] On this, the 21st anniversary of our collaboration, we can think of no more fitting celebration than to have this publication on $d(CH_2)_5Tyr(Me)AVP$ recognized as a *Citation Classic* and to share this honor with the many coworkers who have participated in this journey during the past 21 years.

1. **Berde B & Boissonnas R A.** Basic pharmacological properties of synthetic analogues and homologues of the neurohypophysial hormones. (Berde B, ed.) *Handbook of experimental pharmacology*. Berlin, FRG: Springer-Verlag, 1968. Vol. 23. p. 802-70.
2. **Hruby V J & Smith C W.** Structure-activity relationships of neurohypophyseal peptides. (Udenfriend S & Meienhofer J, eds.) *The peptides*. Orlando, FL: Academic Press, 1987. Vol. 8. p. 77-207.
3. **Sawyer W H, Pang P K T, Seto J, McEnroe M, Lammek B & Manning M.** Vasopressin analogs that antagonize antidiuretic responses by rats to the antidiuretic hormone. *Science* 212:49-51, 1981. (Cited 60 times.)
4. **du Vigneaud V.** Preface. *A trail of research in sulfur chemistry and metabolism and related fields*. Ithaca, NY: Cornell University Press, 1952. p. vii-xi.
5. **Merrifield R B.** Solid phase synthesis I. The synthesis of a tetrapeptide. *J. Amer. Chem. Soc.* 85:2149-54, 1963. (Cited 1,990 times.)
6. **Manning M, Przybylski J P, Olma A, Klis W A, Kruszynski M, Wo N C, Pelton G H & Sawyer W H.** No requirement of cyclic conformation of antagonists in binding to vasopressin receptors. *Nature* 329:839-40, 1987.

IA-20