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Tsou K & Jang C S. Studies on the site of analgesic action of morphine by intracerebral micro-injection. *Sci. Sinica* 13:1099-109, 1964.

[Institute of Materia Medica, Academia Sinica, Shanghai, China]

Microinjection of morphine into the central gray surrounding the third ventricle and aqueduct produced profound analgesia in rabbits with radiant heat as the noxious stimulus. Microinjection of nalorphine into the same area blocked the analgesic action of intravenous morphine. [The *SCI*[®] indicates that this paper has been cited in more than 155 publications.]

The Central Gray and Morphine Analgesia

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The discovery of the central gray as the site of morphine analgesic action was an accident. I was a pharmacology graduate student in China in the late 1950s. My adviser, C.S. Jang, assigned me to study the central effects of autonomic drugs in conscious cats by intraventricular injection—a project with possible implications in central chemical transmissions. Because of the influence of Soviet science in China at that time, he also suggested that I use Pavlovian conditioning as the behavioral index. The conditioning was established by food reinforcement. Soon I found that even intraventricular injection of saline would depress the appetite of the cats, and therefore the conditioned behavior. We tried other behavioral models, including pain.

Since it was not easy to measure a pain response in cats, rabbits were utilized with radiant heat as the noxious stimulus. We then tested analgesics on this model. To our surprise, we found that morphine injected intravenously at one-thousandth of the intravenous (IV) dose produced an equivalent degree of analgesia, which could be blocked by IV nalorphine. Since little was known about the sites of opioid action in the central nervous system in the late 1950s,

and since this observation clearly pointed to the periventricular structures as the sites of morphine analgesia, the use of stereotaxic intracerebral microinjection to locate the sites of morphine analgesic action became my main project.

Through a mapping study, we found that microinjection of morphine into the central gray surrounding the third ventricle and the aqueduct, but not other brain areas, produced profound analgesia. Microinjection of nalorphine into the same area blocked the analgesic action of IV morphine, indicating that the central gray was the main site of morphine analgesia. This work was first published in Chinese in two articles in *Acta Physiologica Sinica*, in 1962¹ and 1963.² Subsequently, by the recommendation of the editorial board of that journal, a combined English version was published in *Scientia Sinica* in 1964—the only English language basic science journal in China at that time. I received many reprint requests from abroad and the paper was first cited by V.J. Lotti et al. in 1965.³ Since then it has been frequently cited, not only because it was a pioneering microinjection study on the sites of opioid action, but also because the area we discovered was later found to have a high density of opioid receptors and opioid peptide-containing nerve terminals, and electrical stimulation of the same area produced strong analgesia. The convergence of experimental data by different approaches was very striking. In brief, this paper helped to shape the concept of an endogenous pain modulation system.^{4,5}

After the opening of China, I traveled extensively abroad. To my surprise, *Scientia Sinica*, the most important science journal in China, could be found only in the central libraries of major universities. This was probably why some colleagues like A. Herz and his coworkers,⁶ who did opioid microinjections in the late 1960s, only obtained my paper through unusual channels after they had finished their own studies.

1. Tsou K & Jang C S. Analgesic effect of intraventricular or intracerebral microinjection of morphine.

Acta Physiol. Sin. 25:119-28, 1962.

2. Tsou K. Antagonism of morphine analgesia by intracerebral microinjection of nalorphine. *Acta Physiol. Sin.* 26:143-50, 1963.

3. Lotti V J, Lomax P & George R. Temperature responses in the rat following intracerebral microinjection of morphine.

J. Pharmacol. Exp. Ther. 150:135-9, 1965. (Cited 155 times.)

4. Kerr F W L & Casey K L. Pain. *Neurosci. Res. Program Bull.* 16:1-207, 1978.

5. Field H L, Barbaro N M & Heinricher M M. Brain stem neuronal circuitry underlying the antinociceptive action of opiates.

Prog. Brain Res. 77:245-57, 1988.

6. Herz A, Albus K, Metys J, Schubert P & Teschemacher H. On the central sites for the antinociceptive action of morphine and

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