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Herz A, Albus K, Metyš J, Schubert P & Teschemacher H. On the central sites for the antinociceptive action of morphine and fentanyl. *Neuropharmacology* 9:539-51, 1970. [Max-Planck-Institut für Psychiatrie, München, Federal Republic of Germany]

Microinjection of opioids into various brain areas and application of opioids into separated parts of the cerebroventricular system in rabbits revealed that complete antinociception can be obtained from caudal parts of the periaqueductal grey and adjacent areas of the floor of the fourth ventricle. [The *SCI*® indicates that this paper has been cited in more than 235 publications.]

The Midbrain as Site of Opioid Antinociception

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Microinjection of opioids into various brain areas and application of opioids into separated parts of the cerebroventricular system in rabbits revealed that complete antinociception can be obtained from caudal parts of the periaqueductal grey and adjacent areas of the floor of the fourth ventricle.

In the late 1960s, when these studies were begun, little was known about sites of action of opioids in the central nervous system, and there were even doubts whether discrete areas may be involved in such complex events as analgesia. Only the high antinociceptive potency of morphine upon intracerebroventricular injection pointed to periventricularly located structures. At that time, Dr. K. Albus in my lab developed a method that, by application of plugs into parts of the cerebroventricular system, allowed the restriction of microinjected drugs to defined areas of the ventricular system in freely moving rabbits. We were very surprised to find that opioid injections into the lateral and the third ventricle did not affect the nociceptive threshold to electrical tooth-pulp stimulation, but were highly effective when applied into the fourth ventricle. Subsequent microinjection experiments[1] pointed to the lower parts of the periaqueductal grey (PAG) and the adjacent parts of the fossa rhomboidea as most sensitive sites of antinociceptive opioid action.

Experiments in which radioactive, labelled opioids were used and their spread in brain tissue was studied autoradiographically supplemented these studies and confirmed the conclusions. These studies also documented the high significance of the physicochemical properties (lipoid-water partition coefficient) of the applied drugs in respect to their spread upon local application and initiated investigations in which the pharmacokinetics of a series of opioids upon systemic and local application were correlated with their hydrophilic/lipophilic properties. While a certain amount of lipophilicity is essential for permeation into the central nervous system, hydrophilicity guarantees that the drug stays at the injection site upon local application. These principles have proved to be essential in optimising the now widely used technique of spinal analgesia.

Initially, experts in neuroanatomy and neurophysiology were somewhat sceptical about our data as more rostrally located areas, e.g., the thalamus, were suggested to be the sites of antinociceptive opioid action. At that time, Professor H. Halbach from the World Health Organization in Geneva—this institution also supported our studies—visited us and we demonstrated these "surprising" data to him. Shortly thereafter he brought a paper to our attention, published in the People's Republic of China a few years before, but not available to us,[2] in which similar, but in detail somewhat different, data were published. In these microinjection studies, which were not complemented by autoradiographic control of the spread of drug, the most sensitive sites of morphine antinociception were located in areas surrounding the third ventricle.

It is now well established that ventrocaudal aspects of the PAG of the midbrain and adjacent parts of the periventricular tissue represent key structures of opioid modulation of pain sensation.[3] These are the same sites from which stimulation-induced analgesia, at least partially reversed by opioid antagonists, can be elicited and descending inhibition of pain transmission in the spinal cord originates.[4]

1. **Herz A & Teschemacher H.** Activities and sites of antinociceptive action of morphine-like analgesics and kinetics of distribution following intravenous intracerebral and intraventricular application. *Advan. Drug Res.* 6:79-119, 1971. (Cited 190 times.)
2. **Tsou K & Jang C S.** Studies on the site of analgesic action of morphine by intracerebral microinjection. *Sci. Sinica* 13:1099-109, 1964. (Cited 150 times.)
3. **Fields H L & Basbaum A L.** Brain stem control of spinal pain transmission neurones. *Annu. Rev. Physiol.* 40:217-48, 1978. (Cited 400 times.)
4. **Yaksh T L & Aimone L D.** The central pharmacology of pain transmission. (Wall P D & Melzack R, eds.) *Textbook of pain.* Edinburgh, Scotland: Churchill Livingstone, 1989. p. 181-205.

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