*European Journal of Pharmacology*, 85 (1982) 121–122
Elsevier Biomedical Press



**Rapid communication**

# DES-TYROSINE-DYNORPHIN ANTAGONIZES MORPHINE ANALGESIA

J. MICHAEL WALKER *, DOUGLAS E. TUCKER, DAVID H. COY **, BARBARA B. WALKER and HUDA AKIL

*Mental Health Research Institute, University of Michigan, Ann Arbor, Michigan, and ** Tulane University School of Medicine, New Orleans, Louisiana, U.S.A.*

Received 1 October 1982, accepted 4 October 1982

Much research has focused on the opiate properties of dynorphin, especially toward differentiating its binding to various receptor sub-populations. The effects of dynorphin in vitro have clearly documented its opiate binding potential. However, central administration of dynorphin produces behavioral and electrophysiological effects unlike those of classical μ-, κ- or δ-receptor agonists. In fact, many of these effects were not reversed by even high doses of naloxone. Such findings are reminiscent of some effects of γ-endorphin which were insensitive to naloxone and could be reproduced with an opiate-inactive fragment, des-Tyr-γ-endorphin (De Wied et al., 1978). We recently showed that a number of electrophysiological and behavioral actions of dynorphin could also be produced by the fragment des-Tyr-dynorphin (Walker et al., 1982). Yet this fragment fails to displace tritiated μ-, κ- or δ-ligands from their binding sites in rat brain homogenates.

One surprising effect of dynorphin was its antagonism of morphine-induced analgesia (Friedman et al., 1981). This effect has been difficult to explain based on classical opiate-receptor models and may be related to its unique non-opiate activity. We show that, the opiate-inactive fragment, des-Tyr-dynorphin, also antagonizes morphine analgesia, supporting a previous suggestion that the in vivo pharmacology of dynorphin has both opiate and non-opiate components (Walker et al., 1982).

Stainless steel cannulas were surgically implanted in the left lateral ventrical of 16 male

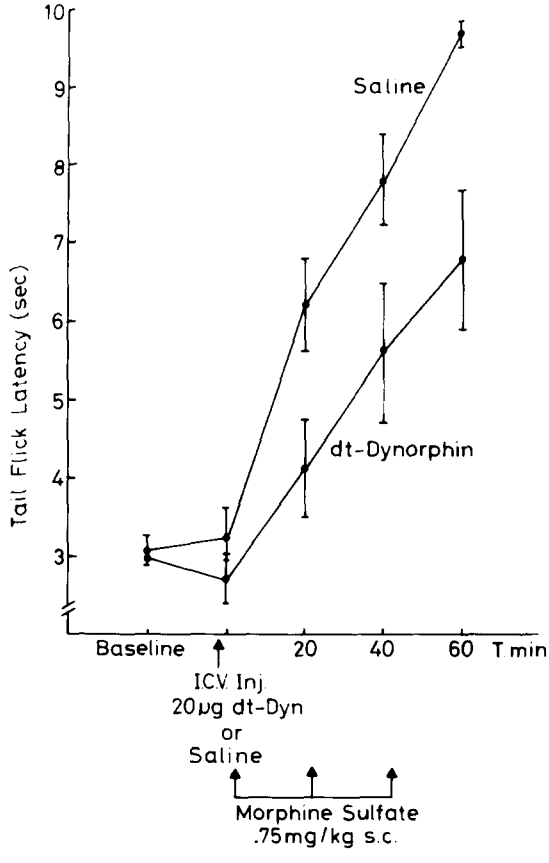


Fig. 1. Effect of intracerebroventricularly administered des-Tyr-dynorphin on morphine analgesia. After recording baseline tail-flick latencies either des-Tyr-dynorphin or saline was administered to separate groups of rats (n = 16). Analgesia was induced over the next 1 h by s.c. injections of morphine sulfate (0.75 mg/kg) at 20 min intervals. Tail-flick testing was conducted just prior to each injection of morphine. Animals treated with des-Tyr-dynorphin exhibited significantly less analgesia than those treated with saline.

* To whom all correspondence should be addressed.

0014-2999/82/0000-0000/$02.75 

Sprague Dawley rats under deep barbiturate anesthesia using methods described elsewhere (Walker et al., 1981). After a week of recovery the animals were tested for pain sensitivity using the tail-flick test of D'Amour and Smith (1941). The tail-flick latency of each animal was recorded before any treatments, then half the animals received des-Tyr-dynorphin (20 μg) and half received the saline vehicle (10 μl) intracerebroventricularly over a 1 min period. The tail-flick latency was recorded again followed by three injections of morphine sulfate (0.75 mg/kg) s.c. given at 20 min intervals in a cumulative dosing paradigm. The development of analgesia was recorded by tail-flick latency prior to each injection of morphine.

The results, illustrated in fig. 1, show that the development of analgesia took place more slowly in the presence of des-Tyrosine-dynorphin compared to the saline vehicle. This effect was confirmed by an analysis of variance ($F1, 14 = 8.04$; $P < 0.01$). A further analysis of co-variance with the baseline trials as the co-variate also indicated a significant effect of des-Tyr-dynorphin in reducing morphine analgesia ($F1, 14 = 7.68$; $P < 0.01$).

These results add support to the previous finding that dynorphin antagonizes morphine analgesia. They further suggest that the opiate sequence within dynorphin is not necessary for the effect and that a second active sequence within the dynorphin molecule is capable of potent effects in vivo. The precise location of this proposed active site is as yet unknown. Nevertheless, it appears that several of the naturally occurring extension of enkephalin contain additional active sequences having a non-opiate character (De Wied et al., 1978).

## Acknowledgements

We wish to thank Giulio Baldrighi and Betty A. Peters for technical assistance and M. Ritchie for manuscript preparation. This work was supported by the following grants: NIDA 1F32DA04183 to J.M.W. and NIDA DA02265, NSF BNS8004512 and the Theophile Raphael Fund to H.A.

## References

D'Amour, F.E. and D.L. Smith, 1941, A method for determing loss of pain sensation, J. Pharmacol. Exp. Ther. 72, 74.

De Wied, D., G.L. Kovacs, B. Bohus, J.M. Van Ree and H.M. Greven, 1978, Neuroleptic activity of the neuropeptide β-$LPH_{62-77}$ (des-Tyr-γ-endorphin: DTγE), European J. Pharmacol. 49, 427.

Friedman, H.H., M.F. Jen, J.K. Chang, N.M. Lee and H.H. Loh, 1981, Dynorphin: A possible modulatory peptide on morphine or β-endorphin analgesia in mouse, European J. Pharmacol. 69, 357.

Walker, J.M., G.G. Berntson, C.A. Sandman, A.J. Kastin and H. Akil, 1981, Induction of analgesia by central administration of ORG 2766, an analog of $ACTH_{4-9}$, European J. Pharmacol. 69, 71.

Walker, J.M., H.C. Moises, D.H. Coy, G. Baldrighi and H. Akil, 1982, Non-opiate effects of dynorphin and des-Tyr-dynorphin, Science (in press).