210

Matsumoto S[1], Goto Y [2], Kogan B A [3], Longhurst P A [4], Levin R M [4], Millington W R [4]
1. Department of Urology, Kinki University School of Medicine, 2. Center for Neuropharmacology and Neuroscience, Albany Medical College, 3. Division of Urology, Albany Medical College, 4. Division of Basic and Pharmaceutical Sciences, Albany College of Pharmacy

OPIOID RECEPTORS IN THE MIDBRAIN PERIAQUEDUCTAL GRAY REGION REGULATE VOLUME-EVOKED MICTURITION

Aims of Study

This study tested the hypothesis that activation of opioid receptors in the midbrain periaqueductal gray (PAG) region inhibits reflex micturition. The PAG plays an important role in the micturition reflex. Activation of neurons in the ventrolateral PAG (vlPAG) with excitatory amino acids induces bladder contraction (Taniguchi et al., 2002) and, conversely, inhibition of neuronal activity with cobalt chloride attenuates volume-evoked micturition (Matsuura et al., 1998). The vlPAG is densely innervated by opioid neurons and activation of mu opioid receptors plays a key role in pain perception and cardiovascular regulation. It is not known whether receptors in the vlPAG influence micturition.

Methods

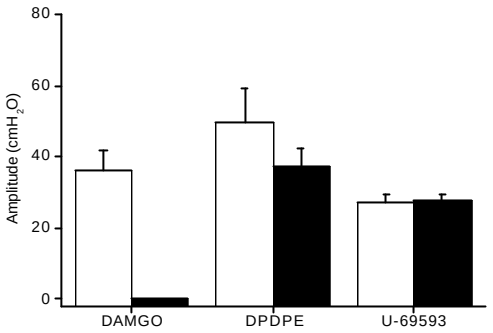
Female Sprague-Dawley rats were anesthetized with urethane (1.2 g/kg), bladder pressure was measured with a transurethral cannula and arterial pressure was recorded through a femoral artery cannula. Continuous cystometrograms were recorded during continuous infusion of 0.9% saline (0.10 ml/min). The amplitude and incidence of bladder contractions and arterial pressure were recorded with a Model 7D Grass Polygraph and analog data were digitized using a Polyview digital analysis system (Grass Instruments, Quincy, MA). Body temperature was maintained at 37.0 $\pm$ 1.0°C.

For intracerebral injections, anesthetized rats were positioned in a stereotaxic frame and a 26-gauge guide cannula was implanted unilaterally in the PAG region at 27^{o} rostro-caudal angle. The tip of the guide cannula was positioned 0.8 mm lateral and 8.3 mm posterior to bregma and 6.7 mm below the skill surface for vlPAG injections and 0.8 mm lateral and 8.3 mm posterior to bregma and 4.6 mm below the skull surface for dorsolateral PAG (dlPAG) injections. Drugs were injected into the PAG in a volume of 0.5 :l over a 60 sec period. Bladder and arterial blood pressure were monitored continuously for 60 min after each injection.

Results

To test the hypothesis that opioid receptors in the vlPAG influence reflex micturition, selective mu, delta or kappa opioid receptor agonists were microinjected into the vlPAG during continuous recording of bladder pressure. Microinjection of the mu receptor agonist DAMGO (0.5 nmol) suppressed volume-evoked bladder contractions completely. The delta opioid receptor agonist DPDPE (0.1 nmol) produced a small but non-significant reduction in the amplitude of bladder contractions (Figure) but did not influence the interval between contractions (data not shown). The kappa agonist U-69593 (0.02 nmol) produced a significant increase in the interval between bladder contractions (data not shown) but caused no discernible change in contraction amplitude (Figure). Microinjection of DAMGO, DPDPE or U-69593 into the dorsolateral PAG did not influence either the amplitude of or interval between bladder contractions. Microinjection of DAMGO into the vlPAG increased arterial pressure significantly but had no effect in the dlPAG/lPAG. DPDPE and U-69593 produced a small but significant pressor response in the vlPAG and a significant depressor effect in the dlPAG/lPAG.

Figure 1. The effect of opioid receptor agonist injection into the vlPAG on the amplitude of reflex bladder contractions. Bladder contractions were monitored for 10 min before (white bars) and 20 after (black bars) microinjection of DAMGO (0.5 nmol) DPDPE (0.1 nmol) or U-69593 (0.02 nmol) into the vlPAG of urethane-anesthetized rats.



Conclusions

These data show that activation of mu opioid receptors in the vlPAG inhibits volume-evoked bladder contraction. Delta opioid receptor activation did not influence micturition significantly but activation of kappa receptors prolonged the interval between bladder contractions significantly. Opioid receptors in the dlPAG apparently do not participate in bladder regulation. These data support the hypothesis that morphine and other opioids cause urinary retention, at least in part, by activating mu receptors in the vlPAG.

References

Matsuura S, Allen GV, and Downie JW. Volume-evoked micturition reflex is mediated by the ventrolateral periaqueductal gray in anesthetized rats. *Am J Physiol Regulatory Integrative Comp Physiol* 275: R2049-R2055, 1998.

Taniguchi N, Miyata M, Yachiku S, Kaneko S, Yamaguchi S, and Numata A. A study of micturition inducing sites in the periaqueductal gray of the mesencephalon. *J Urology* 168: 1626-1631, 2002.