Effects of Naloxone on Renal Responses to Noxious Stimuli in the Cynomolgus Monkey

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ABSTRACT. Behavioral influences on excretion of Na⁺ and H₂O were studied during saline diuresis in three unanesthetized adult female cynomolgus monkeys. During control infusions of isotonic saline, the average rates of urine and Na⁺ excretion were 210 μl/kg/min and 36.1 μl/kg/min, respectively, and the average rate of inulin clearance was 4.6 ml/kg/min. Intermittent exposure to an electrical stimulus applied to the monkey's tail for a 30-min period modestly reduced rates of excretion of Na⁺ and H₂O; these reductions were 58% and 56% of baseline values respectively during the first 10 min, but excretion rates returned to baseline values or exceeded them by the end of the 30-min period. The effects of naloxone hydrochloride (10 mg/kg), an opiate antagonist, were studied by administering the drug immediately before the period of electrical-stimulus delivery. After naloxone, the electrical-stimulus markedly reduced the rates of Na⁺ and H₂O excretion to 29% and 31% of baseline values during the first 10 min, and delayed the return to baseline values. Inulin clearance was not altered significantly by the electrical stimulus in the absence of naloxone, but was decreased to 32% of the baseline rate during the first 10 min of exposure to the electric stimulus in the presence of naloxone. Naloxone had similar effects on rates of Na⁺ and urine excretion in response to 30 min of 108 dBA noise. These results show that renal responses to noxious environmental stimuli (electrical stimulus or noise) can be altered by naloxone.

Key Words: Renal function; Na⁺ and H₂O excretion; Naloxone; Non-human primates; Noxious stimuli.

INTRODUCTION

Studies with laboratory animals have shown renal sensitivity to various types of environmental and behavioral stimuli in the form of alternations in renal blood flow, renal excretion of Na⁺ and H₂O, or plasma renin activity (BLAIR et al., 1976; CLAMAGE et al., 1976; OGLE & LOCKETT, 1968). The role of opiate receptors in renal responses to noxious environmental stimuli has not been studied. There is, however, evidence that specific brain regions such as the mesencephalic central gray, the median eminence, and the hypothalamic regions anteroven tral to the third ventricle are involved in the control of renal function (BRODY et al., 1978; FEIGL, 1964; NICOL & BARKER, 1971; RICHARDSON et al., 1974) and moreover, many of these brain regions have been found to contain either large numbers of opiate receptors (ATWEH & KUHAR, 1977a, b), or high levels of endogenous opiate activity (SIMANTOV et al., 1976). In addition, in the intact rat, both μ and κ opiate receptor agonists have been shown to have significant effects on urine excretion which were blocked by opiate antagonists (HUIDOBRO, 1978; HUIDOBRO-TORO & HUIDOBRO, 1981; LEANDER, 1983a, b). These studies suggest that opiate receptors could be involved in renal responses to noxious stimuli.

The present study investigated the effects of exposure to two types of presumably noxious
stimuli, an electric stimulus and loud noise, on renal excretion of Na\(^+\) and H\(_2\)O in conscious cynomolgus monkeys. The effects of opiate receptor blockade on renal responses to these stimuli were assessed by administering naloxone.

**METHODS**

**SUBJECTS**

Three female cynomolgus monkeys (*Macaca fascicularis*) weighing 2.7 to 3.4 kg were anesthetized with halothane for implantation of indwelling polyvinyl chloride catheters in the mid-abdominal aorta and vena cava. The catheters were passed via the right internal iliac artery and external iliac vein and exited through the skin of the back. The chronically instrumented monkeys were maintained according to procedures described previously (Herd et al., 1969). Animals were housed individually and had unlimited access to food (Purina Monkey Chow) and water, except during experimental sessions. Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and the “Guide for the Care and Use of Laboratory Animals” [DHHS Publication No. (NIH) 85-23, revised 1985].

**APPARATUS AND SAMPLE COLLECTION**

After recovery from surgery (at least ten days) and 24 hrs before each experiment, each monkey was sedated with ketamine HCl (10 mg/kg), fitted with a sterile, pediatric size urethral catheter (Bardex), and seated in a primate chair. The chair was placed inside a temperature controlled, sound attenuating isolation chamber (Model 20, Forma Scientific). Blood and urine samples were collected via tubing outside of the chamber connected to the arterial and urethral catheters.

During studies with the electrical stimulus, a 5-mA, 200-msec stimulus (generated by a 600 V, 60 Hz transformer) was administered to the shaved dorsal surface of the tail 12 times per minute via a pair of brass electrodes coated with electrode paste. The broadband noise stimulus (rapid bursts of 500–20 kHz) was generated by an audiogenerator (Model No. AU902 112–05, BRS/LVE) and was presented via audio speakers attached to either side of the chair about 8 cm from each ear.

**PROCEDURE**

Each 90-min session was divided into three phases: a 30-min baseline period (Phase 1); a 30-min period during which either the electrical stimulus or auditory stimulus could be presented (Phase 2); and a 30-min post-intervention period during which the stimuli were removed (Phase 3). Urine samples were collected at 10-min intervals and blood samples were collected at 10–20-min intervals.

Each of the three monkeys was studied under six different conditions; these conditions were studied in different order with different monkeys. These conditions included: (1) 30 min of exposure to an intermittent electrical stimulus; (2) exposure to 30 min of continuous loud noise (108 dBA); (3) exposure to the electrical stimulus after administration of naloxone HCl in saline (10 mg/kg iv), (4) exposure to the noise stimulus after naloxone, and (5 and 6)