TITLE: ALTERATIONS OF SLOW RESPONSE ACTION POTENTIALS BY SUFENTANIL

AUTHORS: J.R. Blair, M.D., J.K. Pruett, Ph.D., R.P.S. Introna, M.D., R.J. Adams, Ph.D., R.S. Crumrine, M.D.

AFFILIATION: Department of Anesthesiology, Medical College of Georgia, Augusta, GA 30912

INTRODUCTION: Previous studies have shown that sufentanil (SUF) consistently prolongs action potential duration in isolated canine cardiac Purkinje fibers (CCPF).[1] The change seen in the action potential (AP) has been a lengthening in the plateau. Other AP parameters were unchanged. Lengthening of the AP plateau by SUF led us to speculate that the opioid may alter slow inward calcium current (Isi). Consequently, experiments were performed to evaluate the influence of SUF on slow response APs recorded from CCPF.

METHODS: Dogs were anesthetized with 30 mg/kg of pentobarbital IV. Hearts were excised and CCPF were obtained from both ventricles. CCPF were bathed in a 3 ml flow-through bath with oxygenated Tyrode's solution (TS) containing in mM: NaCl, 137.0; KCl, 5.4; dextrose, 5.5; $MgCl_2 \cdot 6H_2O$, 0.5; NaH_2PO_4, 1.8; $NaHCO_3$, 12.0; and $CaCl_2 \cdot 2H_2O$, 1.8. TS flowed at 10 ml/min and was maintained at 37°C±0.2. Microelectrodes were used to record slow response APs in tissue partially depolarized by TS containing 20 mM K^+ and 1.0 μM isoproterenol. The fibers were paced at either 30/min or 12/min after introduction of 20 mM K^+. After control slow response APs were recorded, the fibers were exposed 0.27 μM SUF. Slow response AP's were examined before and after 30 min exposure to SUF and the following AP characteristics were recorded: resting potential (RP), overshoot (OS), amplitude (amp), Vmax (dV/dt of phase 0), and action potential duration at 100% repolarization (APD). Analysis of data was performed using Student's t test of paired data with $p<0.05$ considered significant.

RESULTS: In each case exposure of the depolarized fiber to SUF produced a significant increase in overshoot, amplitude, and dv/dt of the slow AP.

TABLE I
RATE = 30/MIN

Mean N=5	RP	OS	AMP	dV/dt	APD
Control	54.9	0.3	55.2	3.7	181.4
sem ±	1.0	2.9	3.7	0.7	18.6
SUF	53.9	4.8	58.7	4.9	207.6
sem ±	1.3	3.2	4.3	0.8	30.7
p values	NS	<0.05	<0.05	<0.05	NS

TABLE II
RATE = 12/MIN

Mean N=3	RP	OS	AMP	dV/dt	APD
Control	52.3	3.3	55.6	2.7	160.4
sem ±	0.9	3.3	3.1	0.2	11.9
SUF	51.1	7.2	58.3	3.8	190.2
sem ±	1.6	4.7	3.1	0.6	14.7
p values	NS	NS	NS	NS	NS

DISCUSSION: Slow response AP characteristics reflect the underlying calcium current I_{si}.[2] We have shown in these pilot experiments that SUF enhances calcium entry, an effect that was little influenced by moderate changes in rate. The SUF induced changes in OS, AMP and dV/dt were statistically significant in CCPF paced at 30/min but not in CCPF paced at 12/min, a discrepancy that appears to be related to the small N. While the increases in APD of slow APs are not as yet statistically significant, the trend is toward prolongation. We believe that the significance of our results resides in the contribution of Isi to maintaining the AP plateau and thus prolonging AP duration. Of the two main ionic currents responsible for the plateau phase and AP duration, I_{si} and potassium outward current (I_k), I_{si} is believed to be the predominate current.[3] We cannot rule out the possibility that SUF may influence I_k. An increase in I_k would tend to limit the prolongation of the AP duration associated with an increase in the I_{si} and a decrease in I_k would have the opposite effect. On the basis of our results, the increase in I_{si} appears to be at least partially responsible for the prolongation of AP duration effected by SUF in normal fibers.

The statistically significant changes in Vmax and AMP of the slow APs seen in this pilot study indicate that the opioid agonist, SUF, may increase I_{si} at high concentrations. These changes may be similar to those seen with calcium agonist agents. Agents that increase I_{si} may produce an augmentation of contractile force (CF). While data for the direct effect of SUF on CF are lacking, meperidine and fentanyl cause a dose dependent elevation of CF in rat and cat myocardium.[4,5] These changes could be explained by a non-opiate receptor mediated I_{si} agonist effect. The authors believe that SUF produces a prolongation of AP duration in CCPF by an augmentation of Isi during the plateau phase of the AP.

REFERENCES:

1. Blair JR, et al. The Electrophysiologic Effects of Opiates in Canine Cardiac Purkinje Fibers. Anesthesiology 65:A406, 1986.

2. Malécot CO and Trautwein W. On the relationship between V_{max} of slow responses and Ca-current availability in whole-cell clamped guinea pig heart cells. Pflügers Arch. 410:15-22, 1987.

3. Bennett PB and Begenisich TB. Catecholamines modulate the delayed rectifying potassium current (I_k) in guinea pig ventricular myocytes. Pflügers Arch. 410:217-219, 1987.

4. Rendig SV, et al. Comparative Cardiac Contractile Actions of Six Narcotic Analgesics: Morphine, Meperidine, Pentazocine, Fentanyl, Methadone and l-α-Acetylmethadol (LAAM). J. Pharmacol. Exp. Ther. 215:259-265, 1980.

5. Helgesen KG and Refsum H. Arrhythmogenic, Antiarrhythmic and Inotropic Properties of Opioids. Pharmacology. 35:121-129, 1987.