

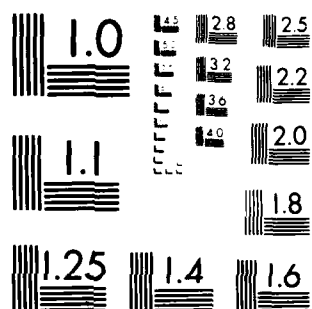
EFFECT OF PFDA ON CARDIAC MEMBRANE FUNCTION(U) WRIGHT
STATE UNIV DAYTON ON DEPT OF PHARMACOLOGY A E LANGLEY
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20./significant fall in the levels of both of these thyroid hormones. It is concluded that PFDA produces an alteration of the normal function of cardiac membranes. This effect may be either direct or indirect via changes in thyroid hormonal levels.



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EFFECT OF PFDA ON CARDIAC MEMBRANE FUNCTION

WRIGHT STATE UNIVERSITY
DAYTON, OH 45435

Dr. Langley

Controlling Office: USAF Office of Scientific Research/NL
Bolling Air Force Base, DC 20332

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Effect of PFDA
on cardiac membrane function

Annual Report

Abstract

The in vivo and in vitro heart rates of rats treated with 75 mg/kg PFDA was significantly lower than the in vivo and in vitro heart rates of pair-fed controls 6 to 8 days following treatment. In addition, the rate response of isolated hearts sympathetic nerve stimulation was greater in the PFDA hearts. Beta receptor binding assays were done on homogenates of hearts from PFDA and pair-fed controls 8 days following a single 75 mg/kg dose of PFDA. PFDA treatment resulted in a significant decrease in the number of cardiac beta receptors. Radioimmunoassays of serum levels of T_3 and T_4 indicate that PFDA produced a significant fall in the levels of both of these thyroid hormones. It is concluded that PFDA produces an alteration of the normal function of cardiac membranes. This effect may be either direct or indirect via changes in thyroid hormonal levels.

I. A time course study of the cardiac effects of PFDA was carried out on rats. Rats were dosed ip. with 75 mg/kg PFDA. A control group of rats was injected ip. with the vehicle used to solubilize PFDA, propylene glycol. The control group was pair-fed to the PFDA group and sacrificed at the same time as the treated animals. Four PFDA and four pair-fed animals were sacrificed on each of the following days after dosing, 2, 4, 6, 8 and 10 days. Hearts with intact sympathetic innervation were removed from the animals. The sympathetic nerves were stimulated electrically with supramaximal voltage, 2msec impulse duration and different frequencies (0.2, 0.4, 0.8, 1.0, 2.0, 4.0 and 8.0 Hz). Cardiac parameters of resting heart rate and resting right ventricular pressure as well as changes in rate and pressure in response to sympathetic nerve stimulation were recorded on a Brush 2400 physiological recorder. In addition, a group of PFDA treated rats was anesthetized with ether and resting in vivo heart rates were recorded. There were no significant differences in either heart rate or ventricular pressure between PFDA and pair-fed controls at day 2 or day 4. From day 6 to 8 both in vivo and in vitro heart rates in PFDA treated rats was significantly lower than in heart rates from pair-fed controls (Tables 1 and 2). In spite of a lower resting in vitro rate, the maximum change in heart rate in response to sympathetic nerve stimulation was significantly greater in the PFDA hearts (Figure 1). There were no differences in resting ventricular pressures. The ventricular pressure response to nerve stimulation was less in hearts from PFDA treated rats. Similar results were obtained at 8 days (Figure 1).

II. The effect of a single 75 mg/kg dose of PFDA on the binding of the β receptor antagonist 3H -dihydroalprenolol (3H -DHA) to cardiac β receptors was tested 8 days following treatment. Rats were decapitated and their hearts rapidly excised, minced and homogenized in ice cold buffer (0.25 M sucrose, 5mM Tris-HCl pH 7.4 and 1 mM $MgCl_2$). The homogenate was filtered through cheesecloth and centrifuged at 480 x g for 10 min. The supernatant was centrifuged at 30,000 x g for 10 min. Following two washings and centrifugation at 30,000 x g the resulting pellet was resuspended in incubation buffer. This was assayed for beta receptor binding using 3H -DHA over a concentration range from 0.1 - 4nM. Figure 2 shows the results of these experiments. There was no change in the K_D value between normal controls

and PFDA treated rat heart β receptors but the maximum number of β (β_{max}) receptors was significantly lower in the PFDA treated hearts. Pair-feeding produced a change in the K_D compared to normal control but no significant change in the number of β receptors (β_{max}).

III. Blood samples were collected from PFDA treated, normal control and pair-fed control rats for determination of serum levels of thyroxine (T_4) and triiodothyronine (T_3) at different times after treatment. Figure 3 shows that as early as 12 hours after PFDA treatment, T_4 levels are significantly lower than both normal and pair-fed control. These levels remained depressed throughout the study. Food restriction in pair-fed control rats resulted in a significant fall in T_4 by day 4. Figure 4 shows similar effect on serum levels of T_3 .

PFDA produces significant alterations of cardiac and endocrine functions in the rat. The precise mechanism of these changes and whether or not they are related remains to be determined.

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Response to Sympathetic Nerve Stimulation

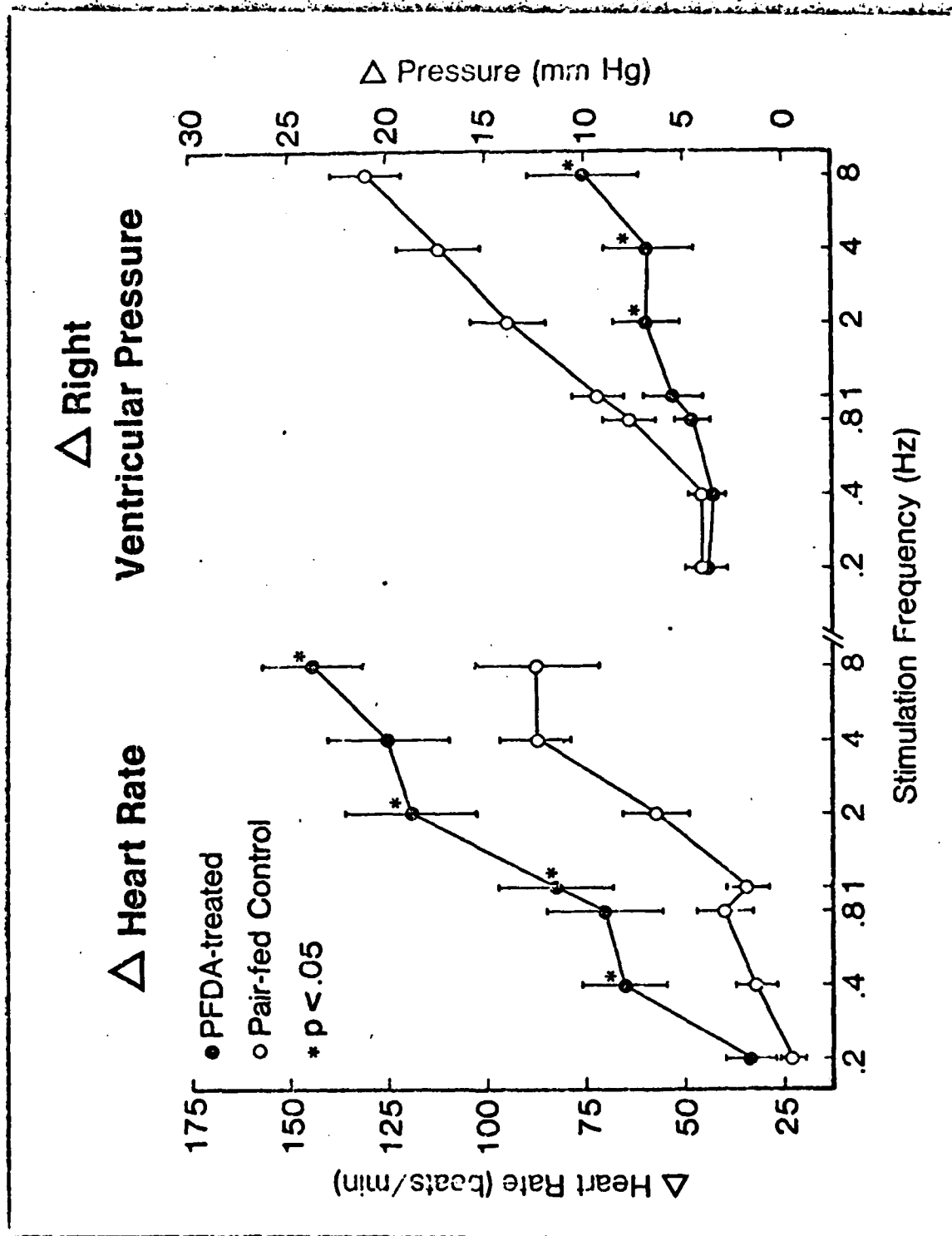


FIG. 1 Change in HR and RVP with nerve stimulation at different frequencies in hearts isolated 8 days following PFDA treatment.

^3H -DHA Binding to rat heart membranes

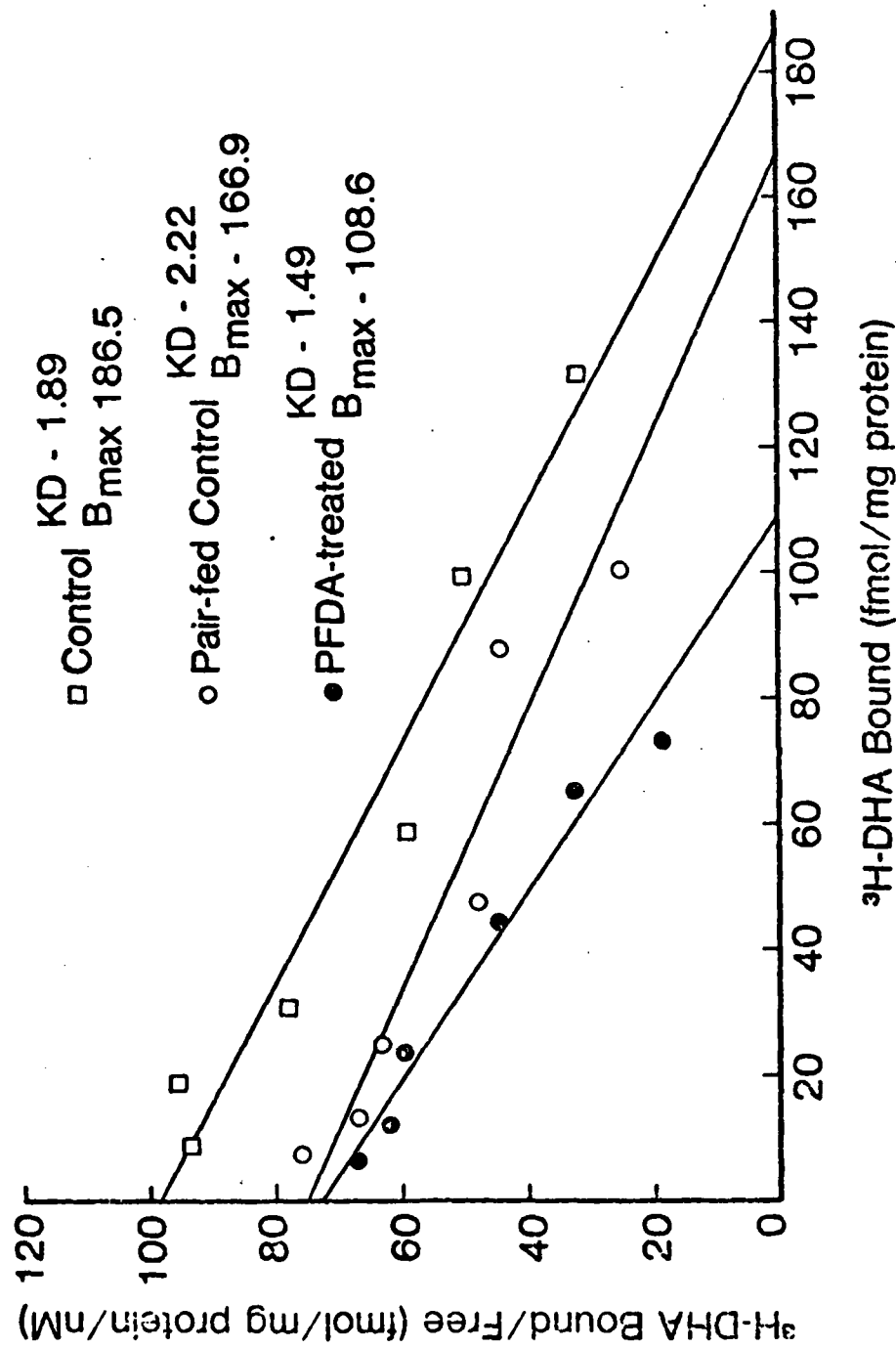


FIG. 2 Scatchard Analysis of ^3H -DHA binding in rat hearts 8 days following PFDA treatment.

PRE-STIMULATION HEART RATES & PRESSURES**

FREQ.	PFDA-TREATED N=6		PAIR-FED CONTROL N=6	
	HR (BEATS/MIN)	P (MM HG)	HR (BEATS/MIN)	P (MM HG)
.2 HZ	169 ± 10*	26 ± 3	226 ± 8	32 ± 3
.4 HZ	178 ± 6*	28 ± 3	226 ± 9	32 ± 3
.8 HZ	187 ± 16	29 ± 3	223 ± 10	30 ± 3
1.0 HZ	181 ± 15*	28 ± 3	226 ± 12	28 ± 3
2.0 HZ	169 ± 7*	27 ± 3	223 ± 11	27 ± 4
4.0 HZ	179 ± 11*	27 ± 3	219 ± 8	27 ± 4
8.0 HZ	171 ± 7*	26 ± 3	222 ± 12	26 ± 3

* P < .05, STUDENT'S "T" TEST.

** THE PRE-STIMULATION VALUES FOR HEART RATE AND PRESSURE WERE DETERMINED WITHIN A 10 SEC. INTERVAL JUST PRIOR TO STIMULATION

TABLE 2
RESTING HEART RATES IN RATS

TREATMENT	ETHER ANESTHESIA		TAIL-CUFF	
	$\bar{X} \pm \text{SEM}$	N	$\bar{X} \pm \text{SEM}$	N
CONTROL	437 ± 13	13	466 ± 16	7
PAIR-FED CONTROL	380 ± 17 ^A	12	322 ± 25 ^A	5
PFDA ^B	330 ± 12 ^C	16	312 ± 25 ^A	5

^ASIGNIFICANTLY LESS THAN AD LIB CONTROLS P < .05

^BHEART RATES RECORDED 7 DAYS FOLLOWING A SINGLE 75MG/KG I.P. INJECTION

^CSIGNIFICANTLY LESS THAN PAIR-FED CONTROLS P < .05

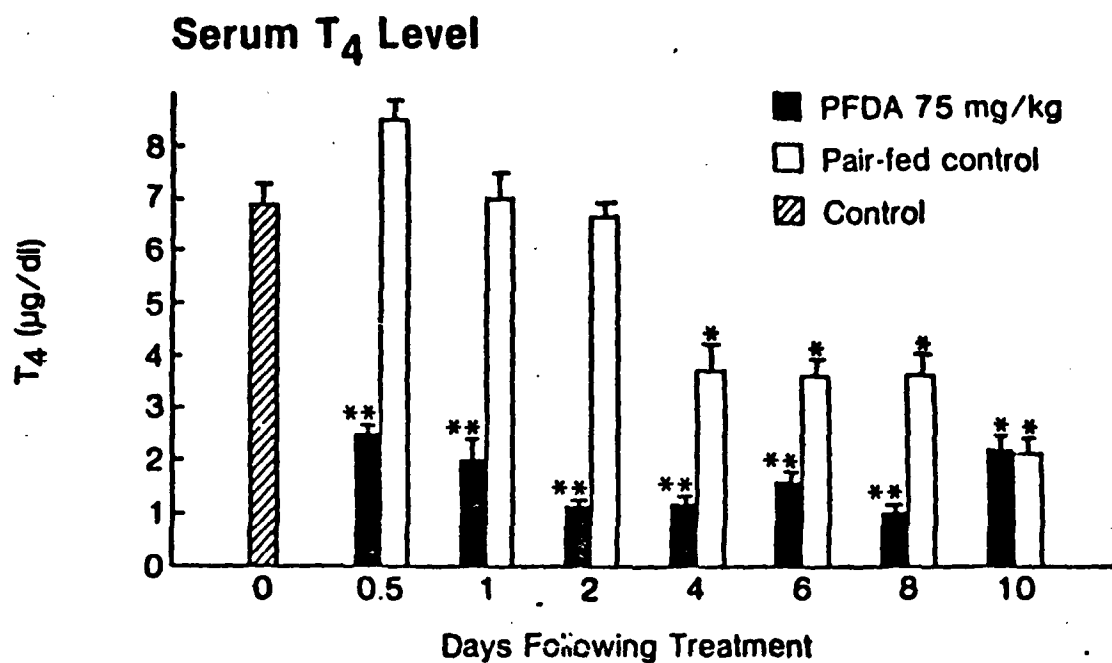


Figure 3

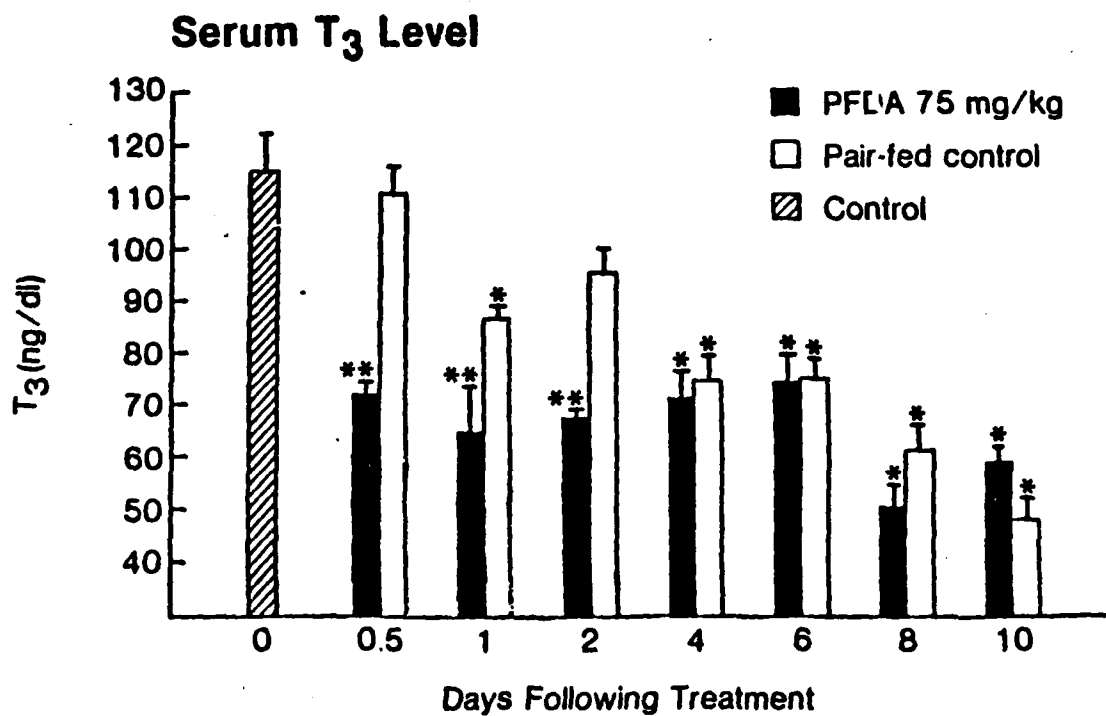


Figure 4

