STIMULATION OF SUBSTRATE OXIDATION IN RAT HEPATIC MITOCHONDRIA FOLLOWING PRETREATMENT WITH APPETITE MODIFYING DRUGS

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D-fenfluramine (Fen) and bupropion (Bup), have pronounced anti-appetite effects (Costa and Garrattini, 1970; Hart-Truax et al, 1983), conversely, cyproheptadine (Cyp) stimulates food intake (Oomura et al, 1973). However, the mechanisms by which these effects are produced have not been elucidated. These experiments investigate the effects of appetite modifiers on mitochondrial substrate oxidation.

Adult male Wistar rats, fed No 1 stock diet and water ad. lib., received either 0.9% saline, 7.5 mg/kg Bup., 5 mg/kg Cyp. or 2.5 mg/kg Fen. i.p. daily for 14 days. Hepatic mitochondria were prepared by the method of Chappell and Hansford (1969). Protein was determined by the method of Gornall et al (1949), oxygen consumption according to the method of McDougall et al (1983) and calcium uptake followed using the method of McNamee et al (1985).

Table I Effect of Appetite Modifying Agents on Substrate Oxidations Associated with Rat Hepatic Mitochondria

Oxygen Consumption (ng atoms oxygen/min/mg protein)

	Glutamate plus Malate		Succinate	
	State 3	State 4	State 3	State 4
Control	34.1 ± 2.7	7.9 ± 0.4	39.5 ± 2.1	14.6 ± 0.3
Cyp.	24.4 ± 2.0*	6.7 ± 0.4n.s.	37.5 ± 1.6n.s.	16.8 ± 0.6*
Fen.	75.9 ± 2.6**	15.8 ± 0.7**	80.7 ± 3.6**	26.8 ± 1.5**
Bup.	56.2 ± 2.8*	11.5 ± 3.0n.s.	73.9 ± 9.3*	29.0 ± 5.0*

n.s. = not statistically significant; * = $p<0.05$; ** = $p<0.01$

Using 5mM glutamate plus 5mM malate both Fen. and Bup. produced statistically significant increases in State 3 and State 4 respiration. In contrast, Cyp. produced only a small change in the State 3 rate (Table I). When 5mM succinate replaced glutamate plus malate a similar pattern was observed. Mitochondria sequester calcium ions by a process dependent on oxidative phosphorylation (Lehninger et al, 1967). Compounds interfering with mitochondrial ATP synthesis modify calcium uptake and release (McNamee et al, 1985). In the presence of 5mM succinate, mitochondria from control animals showed a calcium influx rate of 21.8 ± 4.0 nmoles Ca^{2+}/min/mg protein (n=4), resulting in a total uptake of 9.7 ± 0.5 nmole Ca^{2+}/min/mg protein (n=4), and an efflux rate of 0.5 ± 0.1 nmole Ca^{2+}/min/mg protein (n=4). Neither Fen. or Cyp. produced any changes in mitochondrial calcium transport ($p<0.05$). These results suggest that appetite modifiers may act by an effect on substrate oxidation via the mitochondrial respiratory chain.

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