THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE ACUTE HYPOTHERMIC EFFECT OF D-FENFLURAMINE

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Experiments in this dissertation were conducted to characterize the effects of d-fenfluramine on body temperature and the mechanisms by which d-fenfluramine alter body temperature. The experiments were conducted in conscious male Sprague-Dawley rats. Body temperature was measured in all animals using telemetry. The results of the experiments indicated that d-fenfluramine altered body temperature in animals kept 28, 22, 16 and 4^{o}C. D-fenfluramine produced hyperthermia in animals kept at 28^{o}C and varying degrees hypothermia at normal and cooler ambient temperatures. Further experiments were conducted to explore the effects of d-fenfluramine on brown adipose tissue (BAT) thermogenesis, cutaneous vascular tone and whole body oxygen consumption. In animals kept at 22 and 4^{o}C, we found that d-fenfluramine activated BAT, as indicated by a decrease in BAT norepinephrine content, to the same magnitude. Thus, the hypothermia seen at normal and cooler ambient temperature was not due to lack of BAT activation. Also, activation of BAT by d-fenfluramine was mediated through the sympathetic nervous system and through release of central serotonin, since ganglionic blocker pentolinium and serotonin reuptake inhibitor fluoxetine blocked d-fenfluramine-mediated BAT activation. In animals kept at 16^{o}C, d-fenfluramine increased tail-skin temperature (T_{sk}), an index of cutaneous vascular tone, indicating that d-fenfluramine produced cutaneous vasodilation. d-fenfluramine-induced increase in T_{sk} was mediated through withdrawal of the sympathetic vasoconstrictor tone to the tail, since

pentolinium blocks this effect. In animals kept at 28^{o}C, d-fenfluramine produced a decrease in T_{sk}, indicating vasoconstriction. The effects of d-fenfluramine on the T_{sk} were mediated through release of serotonin, since fluoxetine blocked these effects. D-fenfluramine increased whole body oxygen consumption, an index of metabolic activity and the increase was due to BAT activation, since pentolinium prevented the increase. Thus, although d-fenfluramine increased metabolic activity through BAT activation, the increase was insufficient to make up for the heat loss produced by cutaneous vasodilation and thus produces hypothermia. The hyperthermia seen at 28^{o}C is due to activation of BAT and the subsequent inability of the animal to lose the excess heat due to cutaneous vasoconstriction produced by d-fenfluramine at 28^{o}C.