CIRCADIAN VARIATIONS IN THE ROLE OF NITRIC OXIDE IN THERMOREGULATION, FEEDING AND ACTIVITY IN UNRESTRAINED RATS

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The role of nitric oxide in thermoregulation, feeding behaviour and activity has been studied only during the day and mainly in nocturnally-active animals. Such animals have low daytime food intake, body temperatures and activity levels, which may confound any effects manipulation of nitric oxide may have. Thus, we have investigated whether the effects of decreased nitric oxide synthesis on these three variables is influenced by circadian rhythm in a nocturnal animal, the rat. Individually-caged female Sprague-Dawley rats (200-250 g), housed at ~24°C with a 12:12 h light:dark cycle (lights on 07:00-19:00) and provided with food and water *ad libitum*, were used. We inhibited nitric oxide synthesis by administrating N-nitro-L-arginine methyl ester (L-NAME), a non-specific inhibitor of all nitric oxide synthase isoforms, and aminoguanidine, a relatively selective inhibitor of the inducible isoform of nitric oxide synthase. Four doses of L-NAME (100, 50, 25 and 10 mg/kg) and two doses of aminoguanidine (100, 50 mg/kg) were used. Rats were divided into six groups of six animals each; animals in each group served as their own controls, receiving, in random order, intraperitoneal injections of one of the drug doses or saline during the day (~09:00) or night (~21:00), with seven days between each injection. Body temperature and activity were measured using radiotelemetry; the telemeters were implanted under ketamine: xylazine anaesthesia at least one week before the start of experimentation. Food intake was calculated by weighing each animal's food before and 12 and 24 hours after each injection. Injection of all doses of L-NAME at 09:00 had no significant effect on daytime body temperature, food intake or activity. However, daytime injection of L-NAME decreased nighttime activity (all doses, $P < 0.05$) and food intake (25, 50 and 100 mg/kg, $P < 0.05$), but did not affect nighttime body temperature of the rats. Similarly, injection at 09:00 of either dose of aminoguanidine did not affect daytime body temperature, food intake or activity levels, but decreased nighttime feeding and activity (both doses, $P < 0.05$) whilst not affecting nighttime body temperature. Injection of L-NAME at 21:00 caused eight to ten hours of hypothermia of ~0.6°C, which started one to two hours after injection (50 and 100 mg/kg, $P < 0.05$), reduced that night's activity (25, 50 and 100 mg/kg, $P < 0.05$), and caused a dose-dependent drop in food intake at all doses ($P < 0.05$). On the other hand, injection of aminoguanidine at 21:00 did not cause hypothermia or affect nighttime food consumption, but did reduce that night's activity when the 100 mg/kg dose was injected ($P < 0.05$). The effects of nitric oxide synthase inhibition on body temperature, feeding and activity are therefore influenced by circadian rhythm. Also, inducible nitric oxide synthase may be involved in the regulation of feeding and activity but does not appear to play a role in normal thermoregulation in rats.

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