IMPACT OF TOXIC AGENTS OR ADVERSE CONDITIONS ON THERMOREGULATORY FUNCTION IN AWAKE RODENTS

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In response to exposure to xenobiotic agents, rodents demonstrate significant acute and subchronic decreases in important indices of thermoregulatory and cardiovascular function (termed the *hypothermic response* (Watkinson & Gordon, 1993). These effects are often accompanied by similar decreases in related parameters (e.g., metabolic rate, cardiac output, respiratory rate) and may predispose treated animals to adverse arrhythmic events and lethalities. This response has been observed in a number of studies in our laboratory and appears remarkably consistent, despite the variety of agents (anesthetics, pesticides, ozone, particulate matter, metals, others) and exposure routes (intravenous, intraperitoneal, intratrachael instillation, inhaled) tested. Furthermore, these effects may be modulated by seemingly routine changes in experimental conditions, and are especially sensitive to changes in ambient temperature (T_a) and animal mass. For the most part, these studies used rats that were anesthetized with sodium pentobarbital (50 mg/kg; ip) and implanted with radiotelemetry transmitters capable of monitoring electrocardiogram, heart rate (HR), and core body temperature (T_{co}); at least 7 days were allowed for recovery from these procedures before exposures were conducted. In initial studies, rats exposed to the pesticide chlordimeform (5-60 mg/kg, ip) exhibited acute decreases in T_{co} and HR of approximately 1.0-2.0°C and 50-150 bpm, respectively. In subsequent studies, exposure to ozone (0.5 ppm, inhaled) induced similar decreases in rats maintained at an T_a of 22°C. When the protocol for these ozone studies was repeated at an T_a of 10°C, decreases in T_{co} and HR averaged 2.5-4.0°C and 150-200 bpm, respectively. In similar studies in which mice were acutely exposed to ozone (2.0 ppm, inhaled), T_{co} deficits as high as 10°C were observed. Current studies involving both intratrachael and inhalation exposures of rats to particulate matter and its metallic constituents also induce T_{co} and HR decreases in the ranges of 1.5-3.0°C and 50-150 bpm, respectively, depending on the specific experimental conditions and animal models employed. In companion studies, biochemical indices of pulmonary injury have been shown to correlate well with the magnitudes of these responses. While the underlying mechanism/s remains undetermined, these effects have both physiological and behavioral components and appear to be mediated, in part, via the parasympathetic nervous system. Interestingly, unless severely stressed, humans do not appear to demonstrate this response. Thus, given that rats and mice represent the overwhelming majority of animal species used in toxicological testing, such effects may have important implications with respect to the interpretation and extrapolation of the results obtained from standard toxicological studies.

Watkinson, W.P. & Gordon, C.J. (1993) Caveats regarding the use of the laboratory rat as a model for acute toxicological studies: Modulation of the toxic response via physiological and behavioral mechanisms. *Toxicology* 81: 15-31.

Abstract does not represent US EPA policy.

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