CHAPTER 13

Therapeutic Agents Affecting Body Temperature

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A. Introduction

This chapter surveys the effects on mammalian thermoregulation of general anaesthetics, barbiturates, narcotic analgesics, and phenothiazines, all of which can produce increases as well as decreases in deep-body temperature. In addition to an account of the various factors which influence the degree or direction of temperature change produced by single drug administration, this review contains discussions of how repeated drug administration can give rise to tolerance and of the thermoregulatory changes which may be precipitated by withdrawal of drug treatment. There are also discussions of possible sites and mechanisms of action, of drug effects on heat gain and heat loss mechanisms and of drug interactions giving rise to hyperthermic responses. Drug effects on human thermoregulation have been discussed separately. However, as will be seen, the human data are in general agreement with results obtained in animal experiments.

An important effect of general anaesthetics not discussed in this chapter is malignant hyperthermia. This has been reviewed in Chap. 17.

B. Effects of General Anaesthetics, Barbiturates, Narcotic Analgesics and Phenothiazines on Thermoregulation in Mammalian Species Other than Humans

I. Effects on Body Temperature

1. General Anaesthetics and Barbiturates

At ambient temperatures of 26 °C or less general anaesthetics and barbiturates can lower deep-body temperature in a wide range of species. Falls in deep-body temperature have been observed with pentobarbitone in cats (BANERJEE et al. 1968b; EKSTROM 1951; FELDBERG and LOTTI 1967; FELDBERG and MYERS 1964; STRÖM 1950), dogs (CHATONNET and TANCHE 1957; EKSTROM 1951; HEMINGWAY 1941; STRÖM 1951; HEMINGWAY 1941; KROG 1959), rabbits (FELDBERG and LOTTI 1967), rats (GEMMILL and BROWNING 1962; LOMAX 1966; ISOM et al. 1978), guinea-pigs and hamsters (BRESEE et al. 1975), gerbils (BRESEE et al. 1975; JÄRBE and HOLMGREN 1977), and mice (BRESEE et al. 1975; DANDIYA and SELLERS 1961; HO 1976; MODAK et al. 1976; YAMAMOTO et al. 1978). Hypothermia has also been reported in one or more of these species following administration of amobarbitalone (BRESEE et al. 1975; DAUDOVA 1961; HEMINGWAY 1941), thiopentone and secobarbitone (BRESEE et al. 1975), phenobarbitone (BRESEE et al. 1975; FLACKE et al. 1953; ROSENTHAL 1941),
barbitone (Tahara 1962; Thauer 1943), ethanol (Abdallah and Roby 1975; Carvalho and Izquierdo 1977; Erickson et al. 1978; Flacke et al. 1953; Freund 1973; Järbe and Ohlin 1977; Kakihana 1977; Nikki et al. 1971; Pohorecky et al. 1974, 1976; Pohorecky and Jaffe 1975; Ritzmann and Tabakoff 1976a; Seed and Sechelski 1977; Strömbo et al. 1977; Werner 1941), paraldehyde (Hermann 1941; Rosenthal 1941; Thauer 1943), chloralose (Breese et al. 1975; Feldberg and Lotti 1967; Feldberg and Myers 1964; Thauer 1943), urethane (Grant and Robbins 1949; Hauk and Ankermann 1963), diethyl ether (Hemingway 1948; Lindqvist et al. 1974; Paton and Speden 1965; Pertwee 1970), methoxyflurane (Mäkeläinen 1974; Nikki 1968; Nikki and Tammisto 1968; Paton and Speden 1965; Vapaatalo et al. 1975), halothane (Chambers et al. 1978; Eger et al. 1965; Feldberg and Lang 1970; Mäkeläinen et al. 1973a; Nikki 1968; Nikki and Tammisto 1968; Summers 1969; Vapaatalo et al. 1975), fluoroxene and enfurane (Vapaatalo et al. 1975), cyclopropane (Eger et al. 1965), and nitrous oxide (Pertwee 1970).

The degree and rate of onset of hypothermia induced by general anaesthetics and barbiturates have been shown to be inversely related to ambient temperature (Krog 1959; Lomax 1966; Nikki 1968; Paton and Speden 1965; Pertwee 1970). It has also been shown that at thermally neutral ambient temperatures or above, body temperatures of drug-treated animals usually remain unaffected (Chambers et al. 1978; Freund 1973; Heroux et al. 1956; Mäkeläinen 1974; Mäkeläinen et al. 1973a; Nikki and Tammisto 1968; Pertwee 1970; Vapaatalo et al. 1975) or even rise above control levels (Freund 1973; Thauer 1943). The degree of hypothermia produced by general anaesthetics and barbiturates is influenced not only by ambient temperature but also by dose. Dose-related falls in body temperature have been observed for example in cats with pentobarbitone (Ekström 1951) and chloralose (Feldberg and Myers 1964), in rabbits with amylobarbitalone (Daudoa 1961), in rats with halothane, methoxyflurane (Nikki and Tammisto 1968), and ethanol (Carvalho and Izquierdo 1977), in gerbils with pentobarbitone (Järbe and Johansson 1977) and ethanol (Järbe and Ohlin 1977), and in mice with ethanol (Freund 1973). Dose-related hypothermia has also been observed in mice at an ambient temperature of 20 °C after exposure to diethyl ether, nitrous oxide, nitrogen, argon, dichlorodifluoromethane or chlorodifluoromethane (Pertwee 1970). With all six agents the threshold dose for hypothermia was found to be between one-third and one-fifth of the dose abolishing the righting reflex in 50% of a group of mice. (The loss of the righting reflex of mice is a commonly used, convenient end-point for onset of light anaesthesia). At the lower end of the effective dose range rectal temperatures fell to a new steady level within 60 min and the fall did not exceed 4 °C. At higher doses body temperature was usually still falling after 1 h and hypothermia was greater. With nitrous oxide, dichlorodifluoromethane, and chlorodifluoromethane, falls in temperature greater than 4 °C occurred only at doses equal to or greater than those abolishing the righting reflex.

The existence of a graded relationship between dose and degree of hypothermia suggests that general anaesthetics and barbiturates do not have an "all-or-none" effect on thermoregulation and that at some doses they can alter thermoregulation without completely abolishing it. This suggestion is supported by evidence re-