



A Comparison of Rectal and Subcutaneous Body Temperature Measurement in the Common Marmoset

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Two methods of measuring body temperature were compared in common marmosets. Subcutaneous temperatures were measured remotely via previously implanted subcutaneous microchips (Plexx BV, IPTT-100) prior to measurement of rectal temperature using a conventional rectal probe. Marmosets were treated with saline or the brain penetrant, 5-HT_{1A/B/D} receptor agonist SKF-99101H (3-(2-dimethylaminoethyl)-4-chloro-5-propoxyindole hemifumarate) (0.3–3 mg/kg SC), which has previously been shown to induce hypothermia in guinea pigs. Body temperature was sampled immediately before drug administration and at 30-min intervals thereafter for a period of 2.5 h. SKF-99101H dose-dependently induced hypothermia in the common marmoset and there was close agreement between rectal and subcutaneous body temperatures, with an average difference in absolute body temperature of $0.26 \pm 0.02^\circ\text{C}$. The data show that subcutaneously implanted microchips provide a simple, reliable measure of body temperature in common marmosets which is sensitive to pharmacological intervention, minimizes handling induced stress, and is minimally invasive. © 1999 Elsevier Science Inc.

Key Words: Common marmoset; Subcutaneous temperature; Rectal temperature; SKF-99101H; Microchip

Introduction

Complex thermoregulatory processes are required to maintain body temperature within a narrow range. There have been many nonhuman primate studies of thermoregulation (see Elizondo, 1977 for a review) dealing with a range of topics, e.g., heat balance (Stitt and Hardy, 1971; Johnson and Elizondo, 1979; Stonebrook et al., 1994), diurnal and circadian patterns of body temperature (Liu et al., 1981; Petry and Maier, 1990; Schnell and Wood, 1993; Lane et al., 1996), and the use of body temperature as a pharmacological end point (Rupniak et al., 1992). In these studies various methods have been used to measure body temperature, usually via the rectal or subcutaneous routes. Rectal temperature is usually measured with a rigid steel probe thermometer. The invasive nature of this procedure brings with it some inherent limitations. The stress associated with handling and restraint may itself increase

baseline body temperature (Schnell and Wood, 1993), and repeated sampling increases the risk of rectal bruising and tearing. The thermocouples and radiotelemetry devices used to measure surface/subcutaneous body temperature also involve invasive techniques, although the subsequent need for animal handling is reduced. For example, the thermocouples used by Stitt and Hardy (1971), Johnson and Elizondo (1979) and Liu et al., (1981), were affixed or sutured to the surface of the skin and wired to a recording unit. The radiotelemetry devices used by Petry and Maier (1990), Schnell and Wood, (1993) and Lane et al., (1996) were surgically implanted. Due to their size, microchips can be implanted subcutaneously without anesthesia, hence lengthy surgery and recovery periods are not required and there are no external wires to hinder the movement of the animal. Thus, the use of a microchip with temperature-sensing capacity (BioMedic, IPTT-100) has the potential to reduce the need for animal handling and handling-associated stress and allow for body temperature to be recorded as often as required.

Rectal temperature and body surface temperature are known to differ. Baseline surface body temperature

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has been reported to be 1°–5° C lower than rectal body temperature in some studies (Stitt and Hardy, 1971; Johnson and Elizondo, 1979; Liu et al., 1981). In a circadian rhythm study in rhesus monkeys, the subcutaneous body temperature, measured via radiotelemetry, was approximately 2° C lower than rectal temperature (Lane et al., 1996) and a similar study in common marmosets found that, on average, the subcutaneous temperature was 0.4° C lower than body temperature measured rectally (Petry and Maier, 1990).

The aim of this study was to compare subcutaneous and rectal body temperature of common marmosets under control conditions and after treatment with SKF-9910H (3-(2-dimethylaminoethyl)-4-chloro-5-propoxyindole hemifumarate); a 5-HT_{1A/B/D} receptor agonist which has been shown to induce hypothermia in guinea pigs (Hatcher et al., 1995; Hagan et al., 1997).

Methods

Animals

Twelve Common Marmosets (*Callithrix jacchus*; six male, six female; 4–6 years old; 400–550 g; bred at SB) were used in this study. Marmosets were housed in male/female pairs, under constant temperature ($23.8 \pm 0.13^\circ\text{C}$) and humidity ($42.3 \pm 7.7\%$), on a 06:00–18:00h light cycle and fed Marex pellets (Special Diets Services, Witham, Essex, UK.) and water ad libitum. A diet of mash (made from Marex pellets and condensed milk), fruit, bread, and malt loaf (a bread made with raisins and malt extract) was also fed daily. Animal husbandry and experimentation were conducted in compliance with the Home Office Guidance on the operation of the Animals (Scientific Procedures) Act 1986, and was reviewed and approved by the SmithKline Beecham Procedures Review Panel.

Equipment

The marmosets had BioMedic programmable transponders (microchips, IPTT-100, Plexx BV, 6660 AE Elst, Netherlands) implanted subcutaneously between the shoulder blades. Microchips (approx. 14 mm long, 2 mm diameter; similar to those used in pets for identification purposes) were implanted using the BioMedic Needle Unit, and anesthesia was not required. Readings of subcutaneous body temperature could only be obtained from 11 marmosets and were taken using the handheld BioMedic Pocket Scanner (DAS-5004) held approximately 2 cm away from the microchip. Rectal temperatures were taken using a lubricated clinical thermometer (Philips, HP5316) inserted to a depth of 3–4 cm and left in place until a stable reading was obtained (approx. 1 min).

Procedure

Marmosets were transferred from their home cage to a separate procedure room ($25.3 \pm 0.05^\circ\text{C}$, $36.4 \pm 0.66\%$ relative humidity) and housed individually in familiar holding cages (480 mm \times 270 mm \times 220 mm) with water and food pellets available ad libitum. Here they were allowed to acclimatise for 1 h. All experiments were carried out between 13:00 and 17:00 h.

Subcutaneous and then rectal temperature measurements were taken immediately prior to dosing and at 30-min intervals, thereafter for a period of 2.5 h. Marmosets were dosed with either saline or SKF-9910H (0.3–3 mg/kg SC). The marmosets were returned to the holding cages between temperature readings and to their home cages at the end of each experiment. A period of 48 h elapsed between each test.

Drugs

SKF-9910H was dissolved in 0.05 ml of glacial acetic acid, made up to volume in 0.9% saline and neutralized with 0.05 ml of 2M NaOH. SKF-9910H or 0.9% saline was administered subcutaneously (inner thigh) in a dose volume of 0.2 ml/400 g body weight.

Data Analysis

The effect of SKF-9910H at 0.3, 1, and 3 mg/kg was investigated in three separate experiments. All experiments used a cross-over design in which each marmoset acted as its own control. Temperature changes from time 0 were calculated and subjected to a repeated measures ANOVA followed by Tukey's Studentised Range Test. A paired *t* test was carried on the mean maximum change for each marmoset following vehicle and drug treatment. Correlation coefficients were calculated for the absolute rectal and subcutaneous temperature readings at 60 min post saline and drug administration (SAS-RA; SAS Inc., NC, U.S.A.).

Results

Following saline administration, rectal temperatures ranged from 39.1° to 40.6° C, and subcutaneous temperatures ranged from 38.8° to 41.4° C. There was no statistically significant difference between rectal and subcutaneous temperature change following saline administration (Tukey's Studentised Range Test; Fig. 1–3). Differences between subcutaneous and rectal temperature change during saline and drug conditions are shown in Table 1. On average, subcutaneous temperature was $0.26 \pm 0.02^\circ\text{C}$ lower than rectal temperature. There was a significant overall correlation between the absolute rectal and subcutaneous temperature readings following saline and drug administration, at 60 min postdose ($r =$

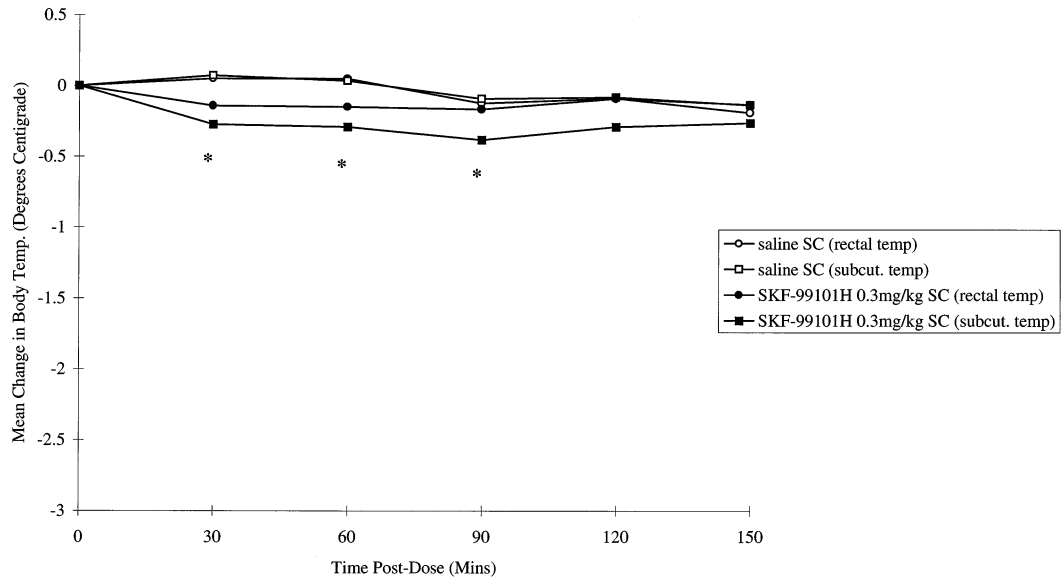


Figure 1. Mean change in rectal and subcutaneous body temperature ($^{\circ}\text{C}$) following saline and SKF-99101H 0.3 mg/kg SC administration. * $p < 0.05$, Tukey's Studentised Range Test, compared to relevant control $n = 11-12$.

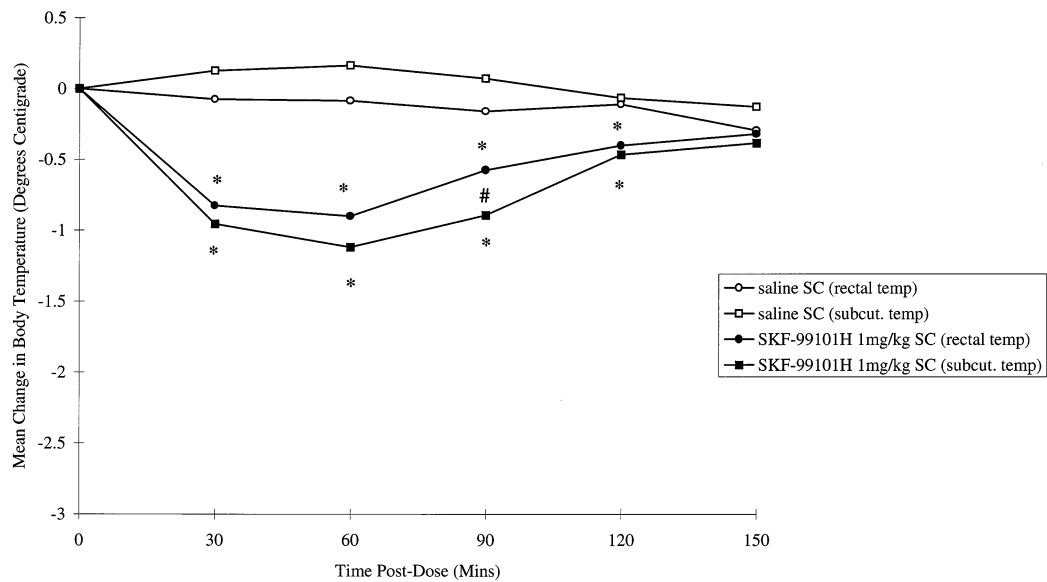


Figure 2. Mean change in rectal and subcutaneous body temperature ($^{\circ}\text{C}$) following saline and SKF-99101H 1 mg/kg SC administration. * $p < 0.05$, Tukey's Studentised Range Test, compared to relevant control. # $p < 0.05$, Tukey's Studentised Range Test, rectal Vs subcutaneous temperature. $n = 11-12$.

0.88, $p < 0.01$, Fig. 4). Further analysis of data from each dosing condition confirmed a positive correlation under all conditions except after SKF-99101H 0.3 mg/kg (Table 2).

SKF-99101H (0.3–3 mg/kg SC) dose-dependently induced hypothermia in the marmoset (Fig. 1–3). At 0.3 mg/kg, there was a significant mean maximal change of

-0.5°C in subcutaneous body temperature compared to baseline (paired t test; $t = 2.395$, $p = 0.038$). Further analysis revealed that this effect occurred at 30–90 min post dose (Tukey's Studentised Range Test; $p < 0.05$, Fig. 1). There was no difference between subcutaneous and rectal temperature readings following SKF-99101H administration.

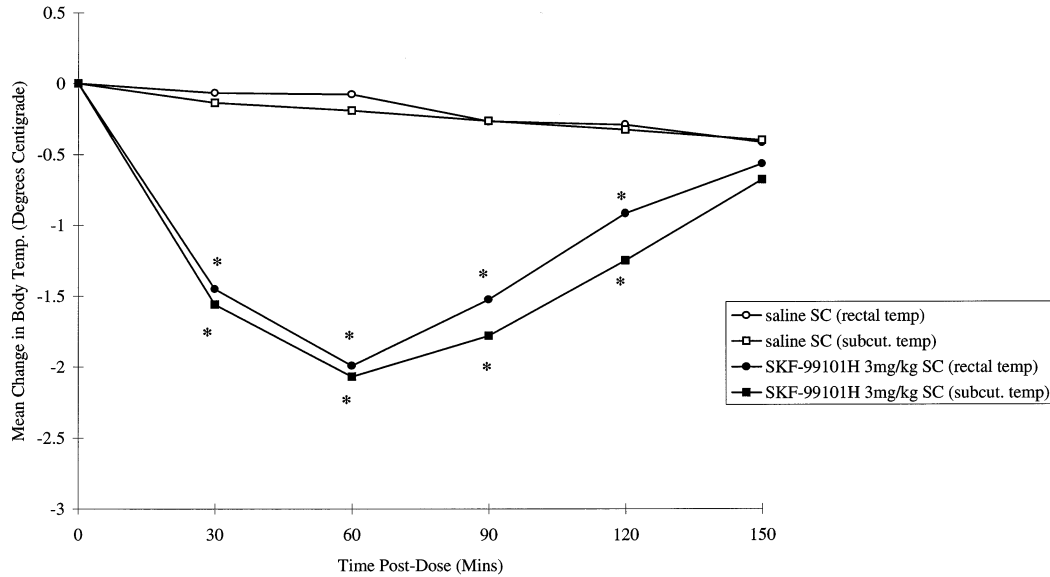


Figure 3. Mean change in rectal and subcutaneous body temperature ($^{\circ}\text{C}$) following saline and SKF-99101H 3 mg/kg SC administration. * $p < 0.05$, Tukey's Studentised Range Test, compared to relevant control. $n = 11$ –12.

Table 1. Differences between mean absolute rectal and subcutaneous temperature readings ($^{\circ}\text{C}$)

	Absolute temperature differences (rectal minus subcut.)					
	Time Post dose (mins)					
	0	30	60	90	120	150
Saline	0.2	0.18	0.22	0.17	0.19	0.14
SKF-99101H 0.3 mg/kg	0.07	0.2	0.21	0.28	0.27	0.2
Saline	0.31	0.1	0.07	0.08	0.27	0.15
SKF-99101H 1 mg/kg	0.24	0.36	0.45	0.55	0.3	0.3
Saline	0.18	0.25	0.3	0.18	0.22	0.17
SKF-99101H 3 mg/kg	0.29	0.4	0.37	0.54	0.62	0.4

Mean (\pm SEM) difference: 0.26 ± 0.02 $^{\circ}\text{C}$.

A significant mean maximal change of -1.0°C in rectal temperature and -1.3°C in subcutaneous temperature, compared to the appropriate saline controls (rectal: $t = 5.046$, $p = 0.0004$; subcutaneous: $t = 7.483$, $p = 0.0001$), was produced following SKF-99101H at 1 mg/kg. Analysis of the time course revealed a significant difference in the two types of temperature readings at 90 min post dose (Fig. 2.) following this dose of SKF-99101H. At this time point, the rectal temperature change was 0.3°C greater than the subcutaneous temperature change (Tukey's Studentised Range Test, $p < 0.05$).

At 3 mg/kg, SKF-99101H induced a significant mean maximal change in both rectal ($t = 8.044$, $p = 0.0001$) and subcutaneous ($t = 6.275$, $p = 0.0001$) body temperatures of -2.0°C compared to relevant controls. No statistically significant difference was seen between subcutaneous and rectal temperature changes following this dose of SKF-99101H (Fig. 3).

The hypothermia induced by 1 and 3 mg/kg of SKF-99101H was significantly different from baseline control at 30–120 min post dose for both types of temperature measurement (Tukey's Studentised Range Test, $p < 0.05$). Peak effect occurred at 60 min post dose, and body temperature had returned to baseline levels by 150 min post dose (Fig. 2, 3).

Discussion

Body temperature measurements taken via the rectal route and the subcutaneous route were in close overall agreement. The data show that treatment with SKF-99101H, a brain penetrant 5-HT_{1A/B/D} receptor agonist, dose-dependently induced hypothermia in marmosets, confirming previous findings in guinea pigs (Hatcher et al., 1995; Hagan et al., 1997). Furthermore, the data clearly show that rectal and subcutaneous temperature readings closely paralleled one another following both

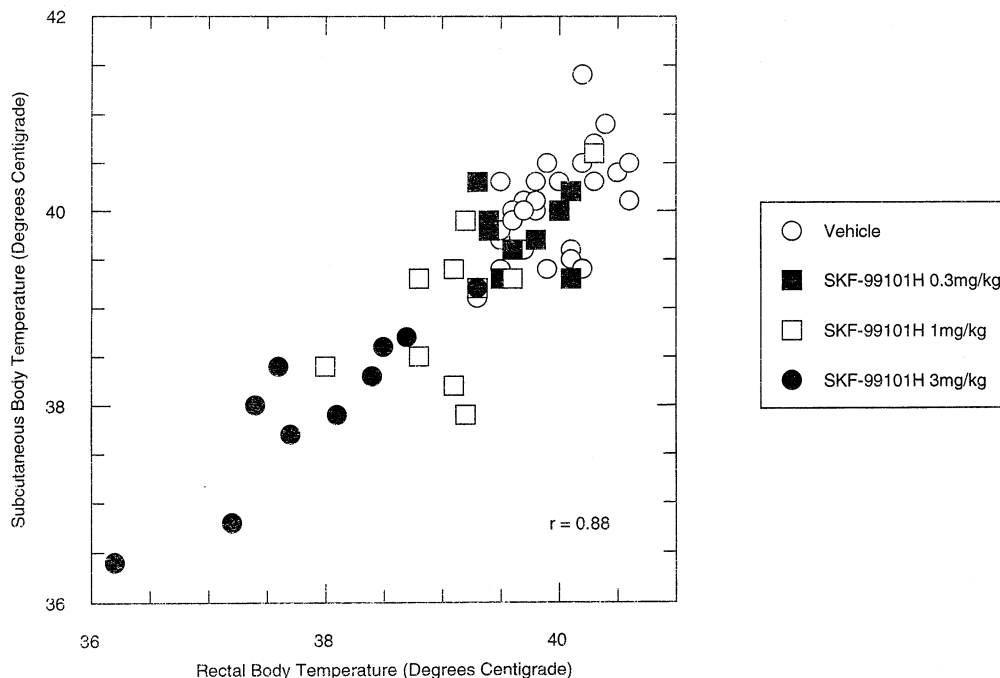


Figure 4. Correlation of absolute rectal and subcutaneous body temperature at 60 min after treatment.

Table 2. Correlation coefficients (*r*) for absolute rectal and subcutaneous body temperatures at 60 min postdose. Saline, *n* = 30; SKF-99101H, *n* = 10.

Treatment	Correlation coefficient (<i>r</i>)	Significance level
Saline	0.51	<i>p</i> = 0.004
SKF-99101H 0.3 mg/kg	0.11	<i>p</i> = 0.762
SKF-99101H 1 mg/kg	0.63	<i>p</i> = 0.049
SKF-99101H 3 mg/kg	0.91	<i>p</i> < 0.001

saline and SKF-99101H administration. One exception was at 90 min post dose, following a dose of 1 mg/kg of SKF-99101H, when a significant difference in mean rectal and subcutaneous temperature change of about 0.3° C did occur. The time course of the hypothermia produced did not differ between the two types of readings, and there was no indication that rectal temperature was returning to baseline levels quicker than subcutaneous body temperature. Previous studies have shown that the hypothermic response to SKF-99101H in guinea pigs is mediated via the 5-HT_{1B} receptor but further work is required to define the 5-HT receptor subtype involved in mediating the hypothermic response to this compound in marmosets.

The large differences seen between rectal and subcutaneous temperature readings in other studies may reflect the method used to measure the subcutaneous temperature. For example, Stitt and Hardy (1971) and

Liu et al., (1981) used thermocouples affixed/sutured to the skin and thus the differences seen may have been due to the cutaneous vasomotor mechanisms involved in thermoregulation. However, the use of radiotelemetry devices still showed a difference of 0.4°–2° C between rectal and subcutaneous body temperatures (Petry and Maier, 1990 and Lane et al., 1996; respectively). This is larger than the average difference produced by the microchips (0.26° C). Although rectal body temperature readings in this study were slightly higher than subcutaneous readings, it is difficult to ascertain if this was due to the stress associated with the procedure or a reflection of the route of temperature measurement. However, the close parallel seen between the rectal and microchip readings strongly suggest that, under the conditions of the present study, subcutaneous body temperature is representative of core body temperature.

This study has demonstrated that microchips with temperature-sensing ability are a reliable, noninvasive alternative to rectal probes.

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References

- Animal (Scientific Procedures) Act (1986). HMSO. ISBN: 0105414867.
- Elizondo R (1977) Temperature regulation in primates. *Int Rev Physiol Environ Physiol* 15:71–118.

- Hagan JJ, Slade PD, Gaster L, Jeffrey P, Hatcher JP, Middlemiss DN (1997) Stimulation of 5-HT_{1B} receptors causes hypothermia in the guinea pig. *Eur J Pharmacol* 331:169–174.
- Hatcher JP, Slade PD, Roberts C, Hagan JJ (1995) 5-HT_{1D} receptors mediate SKF-99101H induced hypothermia in the guinea pig. *J Psychopharmacol* 9(3):192–199.
- Johnson GS, Elizondo RS (1979) Thermoregulation in *Macaca mulatta*: a thermal balance study. *J Appl Physiol* 46:268–277.
- Lane MA, Baer DJ, Rumpler WV, Weindruch R, Ingram DK, Tilmont EM, Culter RG, Roth GS (1996) Calorie restriction lowers body temperature in rhesus monkeys, consistent with a postulated anti-ageing mechanism in rodents. *Proc Natl Acad Sci USA* 93(9):4159–4164.
- Liu CT, Sanders RP, Robbins VW (1981) Diurnal changes in rectal and body surface temperatures of conscious, chair-restrained rhesus macaques. *Am J Vet Res* 42(6):1018–1024.
- Petry H, Maier J (1990) Radiotelemetrische Untersuchungen der Körpertemperatur von Weißbüscheläffchen (*Callithrix jacchus*). *Z Ernährungswiss* 29:197–207.
- Rupniak NMJ, Tye SJ, Iversen SD (1992) Comparison of the effects of selective and non-selective muscarinic agonists on cognition and thermoregulation in primates. *J Neurol Sci* 110:222–227.
- Schnell CR, Wood JM (1993) Measurement of blood pressure, heart rate, body temperature, ECG and activity by telemetry in conscious unrestrained marmosets. *Proceedings of the Fifth FELASA Symposium*. Brighton, UK: Welfare and Science. Ed., J. Bunyan, pp. 107–111.
- Stitt JT, Hardy JD (1971) Thermoregulation in the squirrel monkey (*Saimiri sciureus*). *J Appl Physiol* 31(1):48–54.
- Stonebrook MJ, Weiss HS, Rodriguez-M MA, Rodriguez-M JV, Hernandez-C JI, Peck OC, Wood JD (1994) Temperature-metabolism relations in the cotton-top tamarin (*Saguinus oedipus*) model for ulcerative colitis. *J Med Primatol* 23(1):16–22.