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Spontaneous skin flushing episodes in the aging female rat

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It is well known that with the loss of gonadal function most women experience hot flushes, characterized by a rapid regional increase in cutaneous blood flow. Animal models for this vasomotor syndrome have been elusive, thus hampering efforts to evaluate the endocrine and neuronal substrates of the hot flush. In this report, evidence is reported for the occurrence in aging female rats of spontaneous tail skin temperature (TST) fluctuations which are similar in amplitude, duration and frequency to hot flushes reported for peri-menopausal women. Paradoxically, these TST pulses occur in animals with senescent reproductive states in which serum estrogen levels are moderately elevated and ovariectomy eliminates these rat flushing episodes. This demonstration of steroid-dependent, spontaneous flushing episodes indicates that the aging female rat can be used to evaluate the neuronal and hormonal basis of vasomotor instability.

(Key words: Hot flushes, Aging, Estrogen, Progesterone, Rat)

Introduction

Periods of rapid fluctuations in regional cutaneous blood flow accompany the loss of ovarian function at the menopause in 65–95% of women [1–7]. The resulting hot flushes appear to stem from the inappropriate perception of core body overheating and the consequent activation of heat dissipatory mechanisms [8–10]. An increase in the incidence of this vasomotor instability is associated with the decline in secretion of ovarian estrone and estradiol [11–13], particularly with the free fraction in these circulating steroids [13]. However, subjectively defined hot flushes have been reported in many women prior to the menopause [6,7]. Further, despite similar and large declines of serum levels of estrogens after ovariectomy [14–16] or the menopause [17–20], hot flushes do not occur in all women. The complexity of the steroid involvement in this menopausal syndrome is indicated further by the frequent observation that the incidence of hot flushes decreases with increasing time after the menopause, despite the persistence of low circulating estrogens [6,7]. What is clearly

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needed is an animal model for the hot flush in which the metabolism of and tissue responses to steroids can be evaluated and experimentally altered.

Recently we have reported the occurrence of marked tail skin temperature (TST) surges during naloxone-induced morphine withdrawal in the rat [21]. As in women, each flushing episode in the rat was associated with a transient tachycardia and a surge in the secretion of luteinizing hormone [21]. However, spontaneous flushing activity has not been observed previously in experimental animals. I now report that aging female rats exhibit spontaneous flushing episodes which are associated with reproductive senescence and are dependent upon the ovaries.

Materials and Methods

Female Long–Evans rats were purchased from Blue-Spruce Farms, Altamont, New York, at the ages of 2–3 or 8–10 mth. These animals were housed in an environmentally controlled room separate from all other animals until groups of rats of ages 3–4, 5–7, 16–18, or 33–36 mth were obtained. Vaginal lavages were examined for 15 consecutive days each month to profile the reproductive history of each rat. At the time of the onset of these experiments the 3–4 and 5–7 mth-old groups exhibited normal 4–5 day estrous cycles, the 16–18 mth group had been in constant vaginal estrus or repeated pseudopregnancy for 3–6 mth and the 33–36-mth-old group had been in anestrus for 3–4 mth or repeated pseudopregnancy for 3–8 mth.

To identify spontaneous TST pulses, temperatures were recorded from the tail surface beginning at 30 s after removal of the animals from their home cages and at 5 min intervals for at least 2.5 h thereafter. TST was determined from a surface thermistor (YS1 thermistor probe no. 427) taped on the dorsal surface of the tail at 2 cm from its base. Rectal temperature (T_r) was measured with a YS1 thermistor probe inserted 5 cm into the rectum. Temperatures were recorded on a telethermometer (Model 46 Tuc) while rats were lightly restrained in wire mesh cages, in a climate-controlled room with ambient temperature maintained at 26–27 °C. The cages used were constructed in our laboratory and were designed to provide access ports and to prevent the thermic insulation of typical restraint cages. In each trial, at least one animal from each age group was evaluated.

The parameters of body temperature evaluated were: (1) the initial TST and T_r, (2) mean TST and T_r, (3) coefficient of variation (CV) of TST, and (4) the amplitude of TST pulses observed. The initial TST was that temperature recorded within 1 min of the initial handling and restraint of the rats. The mean TST was obtained by averaging skin temperatures for each animal between 20 and 140 min of observation period. This procedure generally eliminated the initial TST response to stress and more accurately reflects the stable TST in young rats (see Fig. 1). The CV was used to quantify the stability of TST and was calculated as the (mean TST ÷ its standard deviation) $\times 100$ for TST recorded between 20 and 140 min for each animal. To define significant pulses of TST (flushes) during the observation period, I applied a modification of the method used to evaluate pulsatile secretion of luteinizing

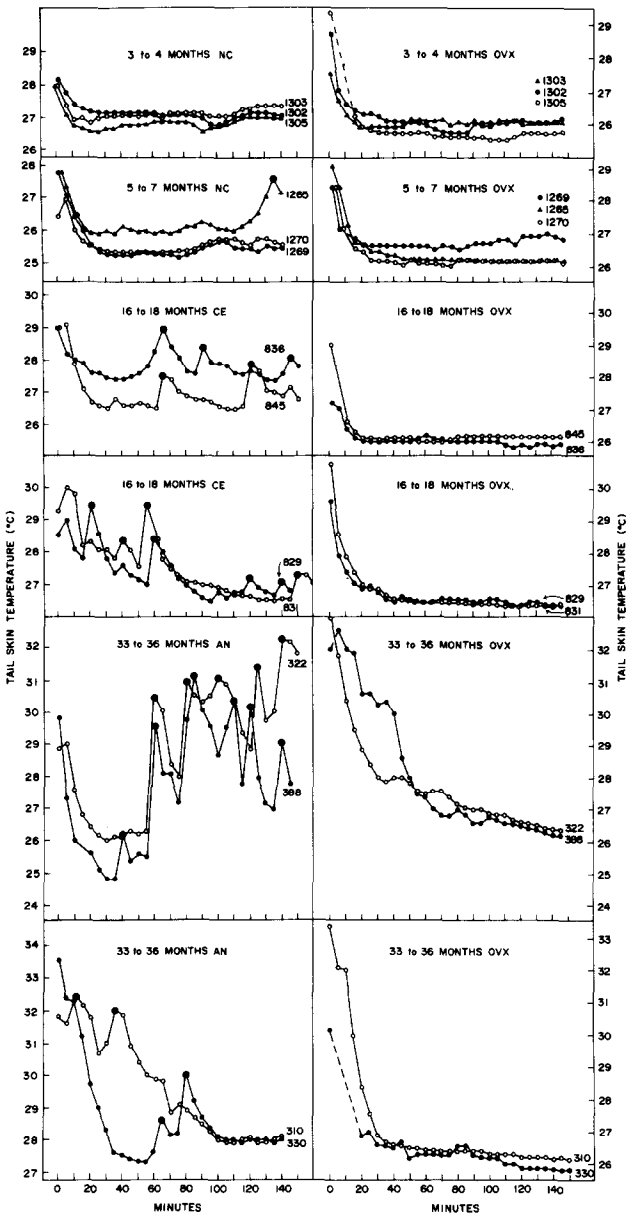

Fig. 1. Tail skin temperature profiles in aging female rats before and after ovariectomy. The left column of panels shows representative TST profiles in four age groups of rats while the right column of panels depicts TST profiles in the same rats at 4 wk after ovariectomy. Rats in the two older age groups which did not exhibit significant flushes are not depicted (see Table I). Bold darkened circles indicate the peaks of significant TST pulses as identified by the methods described in the text. The heading in each panel represents the age range and reproductive status of animals used. NC = normal estrous cycles, CE = constant vaginal estrus, AN = anestrus, OVX = 4 wk after ovariectomy. Animal numbers are indicated next to the TST profile.

hormone in rats [22–25]. Briefly, the CV of the TST of the 3–4-mth-old group of rats was determined and found to be similar to that observed in our studies of other young groups of rats [21,26]. Thus, it was assumed that this CV (0.5 ± 0.04) accurately reflected the stability of TST in young rats maintained in a constant ambient temperature. To determine the significance of an individual TST alteration (flush), the CV of a suspected pulse was evaluated using the skin temperature determinations on both the ascending and descending phases of the pulse. A pulse of TST was considered significant if its CV was greater than twice the CV established for control animals (i.e. CV > 1.0). Applying this criterion, only one of 16 of the young rats (3–4 and 5–7-mth-old) showed a significant flushing episode.

To evaluate for the significance of alteration in these parameters of body temperature, animals were grouped according to four ages (3–4, 5–7, 16–18 and 33–36 mth) and further subdivided according to reproductive status and the occurrence of hot flushes. The temperature recordings were made by a technician who was unaware of animals' reproductive status, and except for the unavoidable observation of increased body weight associated with age, was unaware of the exact age group of the rats. The data were then analyzed by one-way analysis of variance and Student–Newman–Keul's tests. A probability level of $P < 0.05$ was considered significant.

To further assess the influence of reproductive status on TST regulation, animals were bilaterally ovariectomized and skin and core body temperatures were reevaluated 1 and 4 wk later. Data from ovariectomized rats were subjected to analysis of variance and Student–Newman–Keul's tests, as described above.

Two days after the final monitoring period animals were killed by decapitation and necropsies were performed to evaluate for lesions associated with increasing age. Just prior to ovariectomy and at two days following the final monitoring period, a single blood sample (1.0 ml) was obtained by cardiac puncture while rats were under ether anesthesia. Serum was separated and stored at $-80\,^{\circ}C$ until assayed in triplicate for prolactin by the methods described in the NIADDK Kit. All samples were run on a single assay which had a CV of 11.1%. Serum prolactin levels are expressed in terms of the rat RP-1 provided. Differences in serum prolactin associated with age and reproductive status were defined by analysis of variance and Student–Newman–Keul's tests while paired *t*-tests were used to evaluate for effects of ovariectomy.

Results

TST profiles of rats from each of the four age groups revealed a brief increase in TST associated with handling of rats and initial restraint (Fig. 1, left column of panels). In 33–35-mth-old rats, this initial TST response was significantly greater than that observed in the other three age groups (Table I). Following this initial response, young (3–4 and 5–7 mth) rats maintained stable TSTs for at least 2 h (Fig. 1, Table I). In contrast, 4 of 11 of the 16–18 mth-old and 5 of 9 of the 33–35-mth-old rats exhibited spontaneous pulses in TST. The remaining rats in each

TABLE I

EFFECTS OF INCREASING AGE, REPRODUCTIVE STATUS AND OVARIECTOMY ON TAIL SKIN TEMPERATURE (TST) IN THE FEMALE RAT.

Age (mth)	Reproductive status (n)	Flushing (+,−)	Initial TST (°C)	Mean TST (°C)	CV TST (%)	TST pulse parameters (°C)				
						Amplitude	Number			
							0.4–0.9	1.0–1.9	2.0–4.0	> 4.0
3– 4	NC (6)	−	28.3 ± 0.5	27.2 ± 0.1	0.5 ± 0.04	0	0	0	0	0
5– 7	NC (10)	−	28.2 ± 0.5	26.8 ± 0.5	0.8 ± 0.2	1.6	0	1	0	0
16–18	CE (4)	+	29.3 ± 0.2	27.3 ± 0.2	1.9 ± 0.3 [b]	1.1 ± 0.5	6	6	0	0
	CE, PP (7)	−	29.3 ± 0.4	26.6 ± 0.1	0.6 ± 0.1	0	0	0	0	0
33–36	AN (5)	+	31.3 ± 1.0 [b]	28.9 ± 0.5 [a]	4.82 ± 0.9 [a]	2.1 ± 0.2	3	7	7	3
	PP (4)	−	31.0 ± 0.7 [b]	27.1 ± 0.6	1.0 ± 0.1	0	0	0	0	0
3– 4	OVX (6)	−	28.9 ± 0.2	26.3 ± 0.2	0.5 ± 0.1	0	0	0	0	0
5– 7	OVX (10)	−	29.7 ± 0.5	26.3 ± 0.1	0.3 ± 0.1	0	0	0	0	0
16–18	OVX (11)	−	29.4 ± 0.5	26.6 ± 0.2	0.9 ± 0.3	0	0	0	0	0
33–36	OVX (9)	−	31.5 ± 0.5 [b]	26.9 ± 0.3	2.3 ± 0.7 [b]	0	0	0	0	0

Animals in the four age groups were subdivided by reproductive status and the occurrence of flushing episodes. The initial TST is that first temperature recorded after handling of the rats. Mean TST and the CV of TST were determined on the basis of temperatures recorded between 20 and 140 min. This procedure generally eliminated the initial TST response to stress and more accurately reflects stable TST in young rats. The amplitudes of TST pulses are based upon pulses identified by the method described in the text and represent the peak minus the preceding trough temperature. The ovariectomized rats were 4 wk post ovariectomy. Except for one anestrous rat which exhibited a single significant TST pulse, the parameter of TST at 1 wk did not differ significantly from those at 4 wk after ovariectomy. Data were analysed by one-way analysis of variance and Student–Newman–Keul's tests. [a] $P < 0.05$ versus all other groups. [b] $P < 0.05$ versus all groups without this symbol. NC = normal estrous cycles; CE = constant vaginal estrus; AN = anestrus; PP = repeated pseudopregnancy; OVX = 4 wk after ovariectomy.

of the old age groups showed TST profiles which were not significantly different from those of younger rats (Table I).

Pulse analysis revealed that in the four 16–18-mth-old rats, 12 TST pulses were identified while 20 TST pulses were observed in the five 33–35-mth-old rats. The identified pulses were rapid in onset (5–10 min from trough to peak) and usually < 25 min in duration. In the 16–18-mth-old group, all pulses were of low amplitude (< 1.9 °C) while in the oldest age group, pulses were equally divided between low (< 1.9 °C) and high (2.0–4.3 °C) amplitude TST fluctuations (Table I).

Evaluation of reproductive histories for individual rats revealed that for the 33–35-mth-old group all 5 flushing rats were in anestrus while the 4 non-flushing rats were in repeated pseudopregnancy. In the 16–18-mth-old group, all flushing rats were in constant estrus, while the non-flushing group consisted of 5 constant estrous and 2 repeated pseudopregnancy rats.

To assess the contribution of the ovaries to this effect of aging on skin temperature regulation, all rats were bilaterally ovariectomized and TST profiles were evaluated 1 and 4 wk later. Ovariectomy was without effect on TST in non-flushing rats, regardless of their age (Fig. 1, right column of panels, Table I). In contrast, ovariectomy promptly diminished by 1 wk and by 4 wk completely eliminated TST surges in flushing rats (Fig. 1, Table I). Interestingly, the initial TST response to handling and restraint was not affected by ovariectomy, since as observed in intact rats, the 33–35-mth-old group showed an exaggerated TST response to this stress (Table I).

T_r values were recorded throughout the observation period. There was no significant difference among age groups or among animals grouped according to reproductive status. Further, ovariectomy did not alter T_r values of any age group (Table II).

Serum prolactin concentrations, in general, showed an age-related increase. However, because of the high variability in prolactin concentrations in the older age groups and the low number of animals per group, only the 33–36-mth-old anestrus

TABLE II

EFFECTS OF AGE AND REPRODUCTIVE STATUS ON RECTAL TEMPERATURE (T_r) AND SERUM CONCENTRATIONS OF PROLACTIN.

Age (mth)	Reproductive status (*n*)	Flushing (+,−)	T_r (°C) [a]		Serum prolactin (ng/ml)	
			Pre-OVX	Post-OVX	Pre-OVX	Post-OVX
3– 4	NC (6)	−	37.4 ± 0.4 [b]	37.0 ± 0.3 [b]	37 ± 11 [b]	22 ± 5 [b,d]
5– 7	NC (10)	−	37.2 ± 0.2	37.3 ± 0.2	30 ± 7	18 ± 4 [d]
16–18	CE (4)	+	37.7 ± 0.4	37.1 ± 0.4	518 ± 139	63 ± 11 [d]
	CE, PP (7)	−	37.4 ± 0.1	37.1 ± 0.2	156 ± 66	65 ± 14 [d]
33–36	AN (5)	+	37.4 ± 0.2	36.6 ± 0.4	1650 ± 350 [c]	578 ± 342 [d]
	PP (4)	−	37.2 ± 0.2	37.0 ± 0.3	125 ± 12	49 ± 3 [d]

[a] Mean T_r for animals during the 2.5 h observation period.

[b] Mean ± SEM.

[c] $P < 0.05$ vs all other pre-OVX groups as analyzed by analysis of variance and Student–Newman–Keul's tests.

[d] $P < 0.05$ vs appropriate pre-OVX group as analyzed by paired *t*-tests.

Abbreviations used are the same as in Table I.

animals were significantly elevated with respect to all other groups evaluated (Table II). Interestingly, however, if the analysis was confined to flushing vs non-flushing rats of ages 16–36 mth, the flushing rats had significantly higher ($P < 0.025$) serum prolactin levels than age-matched non-flushing rats. All age groups showed a significant decrease in serum prolactin at 4 wk after ovariectomy (Table II). Repeatedly pseudopregnant and constant estrus rats showed a decrease in serum prolactin to levels of about 50 ng/ml. In contrast, old anestrous rats exhibited highly variable prolactin concentration at 4 wk after ovariectomy (range 81–1578 ng/ml serum). Thus at 4 wk after ovariectomy, 4 of 5 anestrous rats had serum prolactin levels at or above those seen in other age-matched rats prior to ovariectomy.

Necropsies were performed to evaluate for the frequently observed anterior pituitary (AP) hypertrophy and hemorrhages in old female rats [27–29]. APs from young rats ranged in wet weight from 8 to 14 mg. Two of 11 of the 16–18-mth-old rats had AP hypertrophy (wet weights of 18 and 24 mg) while the remaining rats showed normal AP appearance and weights (8–13 mg). The 33–36-mth-old repeatedly pseudopregnant rats had AP hypertrophy (wet weight range 14–20 mg) while the anestrous rats had varying degrees of AP hypertrophy and hemorrhage (weight range 16–102 mg). No significant correlations were observed between AP weights and parameters of TST regulation for any of the age groups.

Discussion

The major observation of this study is that 44% of old constant estrous rats and 100% of old anestrous rats exhibit spontaneous TST pulses which are similar in several respects to the hot flushes frequently observed in menopausal women. Quantitative assessments of skin temperature in menopausal women have shown flushes to be rapid in onset (< 10 min), short in duration (20–30 min) and variable in their amplitude (0.5–8.6 °C) [1–5,30]. Similarly, in the aging rat, tail skin flushes were rapid in onset, short in duration and ranged in amplitude from 0.48 to 4.3 °C. To my knowledge, this is the first demonstration of spontaneous skin flushes in an animal model.

The ovarian dependency of these spontaneous TST pulses is indicated by their association with particular senescent reproductive states and the ameliorating effects of ovariectomy. This ovarian contribution could reflect the effects of age on the secretion of specific steroids or the pattern of steroid secretion. In aging constant estrous and anestrous rats, serum estradiol and estrone are maintained persistently at levels of about 20 pg/ml (equivalent to that in young rats on diestrus II of the estrous cycle) while serum progesterone and 20 α-hydroxyprogesterone are low and unvarying [31–33]. By comparison, in repeatedly pseudopregnant rats, estrogens are moderately reduced and serum progestins are persistently elevated [31–33]. It appears, then, that in the aging rat the maintenance of a persistently high estrogen, low progesterone state is associated with TST flushing while a low estrogen, high progesterone environment is not.

The sparing effect of repeated pseudopregnancy on skin temperature regulation in

the rat suggests that elevations in serum progesterone may protect rats from the effects of age or persistent exposure to estrogens on skin temperature regulation. This is not surprising since old repeatedly pseudopregnant rats maintain relative normal LH secretory capacity [34,35] and hypothalamic monoamine metabolism [36], while the old constant estrous rat is much more deficient in this regard [37,38]. However, whether this preservation of normal hypothalamic function reflects an action of progesterone or simply the association of elevated progesterone with low serum estrogens remains to be determined.

The ovarian dependency of rat flushing episodes could also express itself as ovarian-induced changes in anterior pituitary function. In the rat, the hyperprolactinemia observed in constant estrous and anestrous animals is, in part, ovarian dependent. In the present study, we found an association of flushing episodes with animals which were experiencing severe hyperprolactinemia. This is of interest in view of observations that chronic elevations in serum prolactin can affect activity in several neuronal systems in the hypothalamus and preoptic area of the ventral diencephalon [39–42]. The rostral hypothalamus and associated preoptic area are the brain locus of temperature sensitive neurons and are believed to house the brain thermostat [43]. Thus, it is possible that ovarian-induced persistent hyperprolactinemia in the rat causes a dysfunction in skin temperature regulation by affecting these brain centers. We cannot discount, however, the possibility that the elevation in serum prolactin levels observed simply reflects an underlying age-related alteration in the brain which expresses itself as skin temperature instability and hyperprolactinemia. Unfortunately, the response to ovariectomy did not resolve this issue. In the 16–18-mth-old group, ovariectomy reduced serum prolactin to levels seen in non-flushing rats. In the 33–36-mth-old rats, while ovariectomy reduced serum prolactin, levels of the hormone remained elevated in several of the anestrous rats although flushing subsided. Thus, a reduction in serum prolactin level alone was not well associated with the amelioration in skin temperature regulation. An evaluation of serum prolactin concentrations and skin temperature regulation in a larger number of animals is clearly warranted.

Declining gonadal steroid secretion during the peri-menopausal period [6,7,14,41] and the cessation of ovarian estrogen secretion at the menopause [6,7,11–13] appear to establish a propensity for hot flushes in women. This is in marked contrast to flushes in the aging rat which appear to be associated with elevated estrogen levels. Our observation that ovariectomy, which precipitates hot flushes in most women [11–13], eliminates flushing in the rat, indicates a marked species difference in the manner in which an abrupt decline in gonadal secretions influences vasomotor regulation. Elucidation of the mechanism by which these varying steroidal environments manifest themselves as a common vasomotor disturbance may provide useful information as to the mechanism of the menopausal hot flush. Additionally, the aging female rat may be useful in the evaluation of the neuronal substrate for hot flushes and in the initial evaluation of drugs for use in the treatment of this pervasive vasomotor syndrome.

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