Anesthesiology
V 45 No 1, July 1976

Halothane and Calcium Interaction in Isolated Pregnant and Postpartum Rat Myometrium

Nicholas J. Naftalin, M.B., Ch.B.,* W. P. C. Phear, B.Sc.,† Alan H. Goldberg, M.D., Ph.D.‡

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Isolated strips of mid-pregnant and postpartum rat myometrium were rendered functionally Ca^{2+}-free by exposure to a Ca^{2+}-free modified Krebs–bicarbonate solution containing 1 mM EGTA. The muscle strips were then exposed to 2.25 mM Ca^{2+} for periods of 15 to 600 seconds for the mid-pregnant tissues and one 120-second period for the postpartum tissues. At the end of each exposure, Ca^{2+} was removed and simultaneously each muscle was depolarized with 125 mM K_2SO_4. Isometric tension changes in the muscles were measured with and without 0.5 per cent halothane. In the mid-pregnant muscles, halothane diminished the initial tension development in response to Ca^{2+} by approximately 50 per cent, regardless of the duration of Ca^{2+} exposure. The contractile response of these muscles to depolarization with K_2SO_4 was reduced 10 per cent by 0.5 per cent halothane; this was probably due to reduction in transmembrane influx of Ca^{2+}. In the postpartum muscles, the initial tension development in response to Ca^{2+} was threefold greater than in mid-pregnant muscles and was reduced 25 per cent by halothane. These tissues failed to develop any tension in response to K_2SO_4. The most likely explanation for the effect of halothane is that it reduces the transmembrane influx of Ca^{2+} in both types of tissues, but that the postpartum sarcoplasmic reticulum presents less competition for intracellular Ca^{2+} than pregnant sarcoplasmic reticulum. **(Key words: Anesthetics, volatile, halothane; Uterus, contractility; Ions, calcium; Anesthesia, obstetric.)**

* Lecturer, Department of Obstetrics and Gynecology, University of Leicester, Leicester, U.K.; formerly, Research Fellow in Anesthesia, Harvard Medical School, Boston City Hospital.

† Associate in Anesthesia, Harvard Medical School.

‡ Professor and Associate Chairman, Department of Anesthesiology, Boston University School of Medicine; Clinical Director, Department of Anesthesiology and Director, Anesthesia Research Laboratory, Boston City Hospital.

Received from the Anesthesia Research Laboratory, Boston City Hospital, Boston, Massachusetts 02118. Accepted for publication February 27, 1976. Supported in part by grants from The Medical Foundation, Inc., of Boston, and the National Institute of Child Health and Human Development (Grant No. 5RO1 HD05935).

Address reprint requests to Dr. Alan H. Goldberg, Boston City Hospital, Boston, Massachusetts 02118.

TENSION DEVELOPMENT in smooth muscle depends upon the myoplasmic calcium level, which reflects both transmembrane influx and efflux of calcium, and the uptake and release of this ion from intracellular calcium-buffering organelles.[1,2]

Previous studies from this laboratory[3] have indicated that halothane causes uterine atonicity primarily by affecting the calcium-dependent component of resting tension. This loss of tone occurs even with low halothane concentrations. Its speed of onset suggests that a superficial site of action on the muscle is involved, and halothane has been shown to affect the cell membrane.[4] A reasonable explanation for the marked depressant effect of halothane on a tonic muscle

ABBREVIATIONS

- Ca time = duration of exposure to calcium
- +dP/dt = maximum rate of tension development
- −dP/dt = maximum rate of tension relaxation
- EGTA = ethylene glycol bis (B-amino ethyl ether) N,N'-tetraacetic acid
- I_1 = tension–time integral of initial response to calcium
- I_2 = tension–time integral of rising portion of K_2SO_4-induced contraction
- I_3 = tension–time integral of falling portion of K_2SO_4-induced contraction
- S = a modified calcium-free Krebs–bicarbonate solution containing EGTA
- S − E = S minus EGTA
- SCa = S with calcium; EGTA absent
- SK = S with K_2SO_4; EGTA absent
- SR = sarcoplasmic reticulum
- T_{Ca} = mean initial tension response to calcium (mean I_1 divided by Ca time)
- T_K = peak tension developed above resting tension in response to K_2SO_4

such as the uterus could be a diminished membrane permeability to calcium. However, there have been no studies of the effects of halothane on calcium flux across the sarcolemma.

In the present experiments, the mechanical responses of "calcium-free" pregnant and postpartum muscle to a limited exposure to calcium, and the effects of low halothane concentrations thereon, were measured. Postpartum strips were studied to determine whether there are any differences between their physiologic behavior and that of pregnant muscle, and whether there are any differences in their responses to halothane. The experimental design permitted the assumptions[3] that a) the observed mechanical changes reflected alterations in transmembrane influx of the calcium ions, which are involved in activation of the contractile proteins, and b) the effects of halothane on mechanical properties are due, at least in part, to its influence on transmembrane movement of Ca^{2+}.

Methods

Seventeen pregnant and eight postpartum white Sprague-Dawley rats (250–300 g) were studied. Estimation of the periods of gestation of the pregnant animals was based on the dates of mating and the sizes of the products of conception. Specimens were taken only from animals 7 to 14 days pregnant. The postpartum animals were studied within 36 hours of delivery.

Following decapitation, anteplacental strips of uterus were obtained. After the intraluminal surface was gently scraped free of membrane and decidua, each strip was trimmed to approximately the same length and cross-sectional area. It was then suspended between two ring clamps in a 12-ml muscle bath containing a modified Krebs–bicarbonate solution (S) that lacked calcium but contained EGTA. (EGTA removes Ca^{2+} by chelation.) The composition of S in mM was: NaCl 120; $NaHCO_3$, 25; NaH_2PO_4, 1.38; $MgSO_4$, 1.2; dextrose 11.1; KCl 5.0; EGTA 1.0.

The following modifications of solution S were used during the experiment:

S – E : S without EGTA
SK : S with 125 mM K_2SO_4; KCl and EGTA absent
SCa : S with 2.25 mM $CaCl_2$; EGTA absent

The bath was constantly perfused with a 95 per cent O_2–5 per cent CO_2 gas mixture with or without halothane; anesthetic concentrations were measured by gas chromatography. The mean halothane concentration was 0.51 per cent (range 0.30 to 0.70 per cent). Thermostatic control of water in tubing surrounding the water bath maintained the temperature of the fluid in the bath at 20C. The *p*H was 7.4.

Muscle tension was detected with an isometric tension transducer (Statham UC-3), amplified, displayed on an oscillographic recorder, and stored on light-sensitive paper.

During the equilibration period of approximately an hour, solution S was periodically replaced by solution SK, which induced depolarization. SK depolarizations were repeated until no isometric response was elicited; this indicated that the muscle strip was functionally calcium-free. Resting tension was maintained at about 0.5 g by continuous adjustment of the muscle length. After equilibration, muscle length was held constant.

In order to ensure that the muscle response was not affected by a residuum of EGTA in the muscle bath during the timed exposure to calcium, EGTA was removed before each calcium exposure by a double wash with solution S-E. After a 6–8-minute interval, each muscle was then exposed to calcium (for various periods of time) by replacing solution S-E with SCa. The durations of calcium exposure (Ca times) were 15, 30, 60, 120, 300, and 600 seconds for the pregnant muscles and 120 seconds for postpartum muscles. The sequence of calcium exposure times was completely randomized. Each muscle was depolarized by rapid replacement of SCa with SK (which was calcium-free).

When the tension response to the K_2SO_4 depolarization had decayed by at least 75 per cent, the muscle was double-washed with solution S and left for 10 minutes. During

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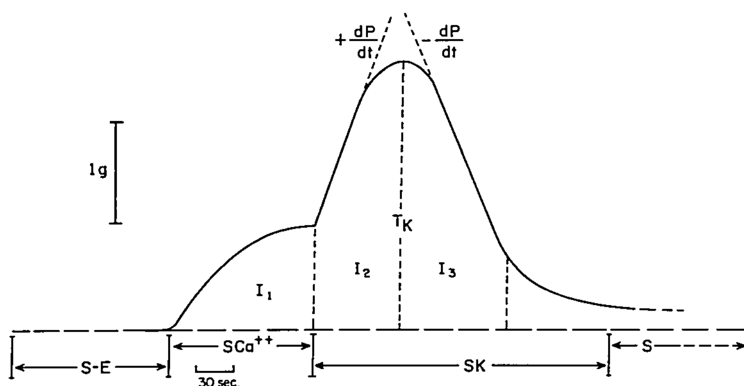

FIG. 1. Diagrammatic sequence of pregnant muscle responses. Solution S (Krebs with EGTA; no Ca^{2+}) was used for equilibration between contractions. EGTA was removed by the use of S-E. The muscle was then exposed to calcium (SCa). I_1 is the tension–time integral of the initial exposure to Ca^{2+}. Depolarization was then achieved with SK that contained K_2SO_4 but no Ca^{2+}. When relaxation was 90 per cent complete, the bath was refilled with S. The rate of rise of tension (+dP/dt) and the peak tension (T_K) developed during this contraction were measured. The tension–time integral of the rising portion of this K^+-induced contraction was expressed as I_2. Also measured were the rate of decline of tension (−dP/dt) and the tension–time integral (I_3) at 75 per cent decline of T_K.

this period, replacement of S by SK indicated no contractile response. A 6–8-minute exposure to S-E solution then preceded another Ca time. This entire sequence was repeated with and without halothane.

The sequence of study at each Ca time was: no halothane, 0.5 per cent halothane, no halothane. Each muscle was washed with solutions S and S-E. Because each muscle was studied in O_2–CO_2 before and after exposure to 0.5 per cent halothane, each muscle served as its own control.

In the pregnant muscles, the tension–time integral of the initial response to calcium during each Ca time (fig. 1) was expressed as I_1 (kg-sec/cm^2). An attempt to compare maximal tension developments during calcium exposure at each Ca time proved difficult due to variation in the rates of tension development and undulations in tension once the maximum tension was attained (particularly at the longer Ca times). For convenience in interpreting changes in tension at different Ca times, T_{Ca} (kg/cm^2) was calculated as mean I_1 divided by Ca time. The peak tension (T_K) developed above resting tension in response to K_2SO_4 was measured (g/cm^2), as were the rates of rise (+dP/dt) and fall (−dP/dt) of tension (g/sec/cm^2). The integrals of the rising portion from onset to peak of the K_2SO_4-induced contraction (I_2), and the falling portion, from the peak of the contraction to the time at which tension had decayed by 75 per cent (I_3), were also measured (kg-sec/cm^2).

In the postpartum muscles, the absence of contraction in response to K_2SO_4 depolarization removed T_K, I_2 and +dP/dt from the analysis. Accordingly, I_1, I_3, and −dP/dt were measured as described for the pregnant muscles.

At the end of each experiment, muscle length was measured. The average length for the pregnant tissues was 5.6 mm ± 1.5 (SE); for the postpartum tissues it was 11.3 mm ± 1.2. Each muscle was dried overnight, weighed, and its cross-sectional area (CSA) calculated based on a specific gravity

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TABLE 1. Mechanical Responses of Ca^{2+}-free Myometrium to Ca^{2+} with and without 0.5 Per Cent Halothane (Means ± SEM)*

	Pregnant Myometrium, Duration of Exposure to Ca^{2+}						Postpartum Exposure 120 Sec
	15 Sec	30 Sec	60 Sec	120 Sec	300 Sec	600 Sec	
I_1 (kg-sec/cm²)	0.278 ± 0.083	0.897 ± 0.182	5.674 ± 0.972	26.022 ± 6.595	110.354 ± 42.29	218.020 ± 130.940	73.99 ± 7.46
Δ†	−69 per cent, $P < 0.02$	−34 per cent, $P < 0.05$	−47 per cent, $P < 0.01$	−52 per cent, $P < 0.02$	−59 per cent, $P < 0.02$	−49 per cent, NS‡	−24 per cent, $P < 0.01$
T_K (g/cm²)	150.5 ± 8.1	166.9 ± 14.1	206.6 ± 17.7	223.9 ± 19.9	249.5 ± 16.8	273.5 ± 26.4	—
Δ	−18 per cent, $P < 0.02$	−24 per cent, $P < 0.02$	−10 per cent, $P < 0.05$	−11 per cent, $P < 0.001$	−8 per cent, $P < 0.001$	−10 per cent, $P < 0.01$	— —
I_2 (kg-sec/cm²)	5.75 ± 0.36	7.02 ± 0.73	8.67 ± 0.51	12.36 ± 1.11	13.07 ± 1.22	14.76 ± 1.19	—
Δ	−20 per cent, $P < 0.02$	−24 per cent, $P < 0.05$	−8 per cent, NS	−15 per cent, $P < 0.01$	−16 per cent, $P < 0.01$	−19 per cent, $P < 0.02$	— —
+dP/dt (g-sec/cm²)	21.2 ± 4.6	25.7 ± 4.7	31.2 ± 4.8	31.8 ± 6.4	29.1 ± 4.4	33.0 ± 6.8	—
Δ	−26 per cent, $P < 0.001$	−25 per cent, $P < 0.05$	−19 per cent, NS	−18 per cent, $P < 0.05$	−4 per cent, NS	−11 per cent, NS	— —
I_a (kg-sec/cm²)	14.55 ± 0.94	19.00 ± 2.15	34.73 ± 8.85	67.51 ± 4.83	83.80 ± 7.71	135.68 ± 12.57	16.32 ± 3.19
Δ	−24 per cent, $P < 0.01$	−35 per cent, $P < 0.01$	−23 per cent, NS	−32 per cent, $P < 0.01$	−37 per cent, $P < 0.01$	−37 per cent, $P < 0.01$	−23 per cent, $P < 0.05$
−dP/dt (g-sec/cm²)	1.20 ± 0.74	0.70 ± 0.17	0.99 ± 0.65	3.37 ± 2.39	1.87 ± 0.58	2.31 ± 0.34	0.65 ± 0.12
Δ	−6 per cent, NS	−10 per cent, NS	+1 per cent, NS	−1 per cent, NS	+13 per cent, NS	+10 per cent, NS	−23 per cent, $P < 0.05$

* n = 6 for each Ca exposure.
† Δ = Change with 0.5 per cent halothane.
‡ NS = not significant.

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of 1.054.[5] The average CSA was 1.28 mm^2 ± 0.21 (SE) in the pregnant group, and 0.96 mm^2 ± 0.10 in the postpartum specimens.

All results were corrected for CSA. The statistical analyses used were Student's t test and least-squares regression, with $P < 0.05$ taken as the level of significance.

Results

Pregnant Muscles

During exposure to calcium, tension gradually rose towards a plateau value. The integral of this tension over time (I_1) increased with duration of exposure to calcium (table 1). The corresponding plot of T_{Ca} (fig. 2) rose slowly for the first 30 seconds and thereafter rose exponentially for Ca times to 300 seconds.

T_K and I_2 increased exponentially with increasing exposure to calcium (table 1). The change of +dP/dt *vs.* Ca time was exponential to 60 seconds and then became constant.

In the relaxation stage following the K_2SO_4-induced contraction, I_3 increased with increased time of exposure to calcium. −dP/dt varied considerably from muscle to muscle, and no consistent response could be demonstrated.

In the 60–600-second calcium exposures, T_K was reduced a constant 8 to 11 per cent by halothane (table 1). In the 15- and 30-second exposure groups, T_K declined by 18 and 24 per cent in the presence of halothane. Reductions in both +dP/dt and I_2 paralleled the halothane-induced changes in T_K in all exposure groups.

I_3 was significantly depressed (23–37 per cent) by halothane in all exposure groups; −dP/dt was unaffected (table 1).

Halothane decreased T_{Ca} by approximately 50 per cent regardless of the duration of exposure to calcium (fig. 2).

Postpartum Muscles

The response of the postpartum muscles to a 120-second exposure to calcium is shown in figure 3. No additional tension response was obtained when these muscles were depolarized with the calcium-free K_2SO_4 solution. I_1 was reduced by 24 per cent in the presence of halothane. During the relaxation stage both I_3 and −dP/dt were reduced 23 per cent by halothane.

Pregnant versus Postpartum Muscles

Comparisons between pregnant and postpartum muscles were made at the 120-second Ca time. The major difference was the complete lack of K_2SO_4-induced tension development after exposure to calcium in the postpartum muscles compared with the 224 g/cm^2 T_K response obtained in the pregnant tissues (figs. 1 and 3). The tension–time integral (I_1) of the response to 120 seconds of calcium exposure was nearly three times larger ($P < 0.001$) in the postpartum compared with the pregnant muscles (table 1). The 52 per cent depression of I_1 induced by halothane in the pregnant group, however, was double that found in the postpartum muscles (−24 per cent; $P < 0.01$).

Due in part to the lack of a tension response to K_2SO_4 in the postpartum tissues, the control values for the relaxation modalities started from greatly reduced levels in this group compared with the pregnant muscles (table 1). I_3 was 76 per cent less ($P < 0.01$) and −dP/dt was 81 per cent less ($P < 0.01$) in the postpartum specimens.

There was no statistically significant difference between the effects of halothane on I_3 in the pregnant and postpartum tissues. Halothane exerted a greater depression in −dP/dt in the postpartum, compared with the pregnant, muscles ($P < 0.05$).

Discussion

Due to the time constraints of the experimental protocol, and also because no developed tension (T_K) was produced in postpartum muscles, it was not possible to perform length–tension studies. Therefore, the same low resting tension was chosen for all muscles to assure that they would all be on the ascending limbs of their respective length–tension curves.

The myometrial strips used in this experiment were initially rendered calcium-deficient by prolonged exposure to EGTA in a calcium-free medium (solution S). EGTA,

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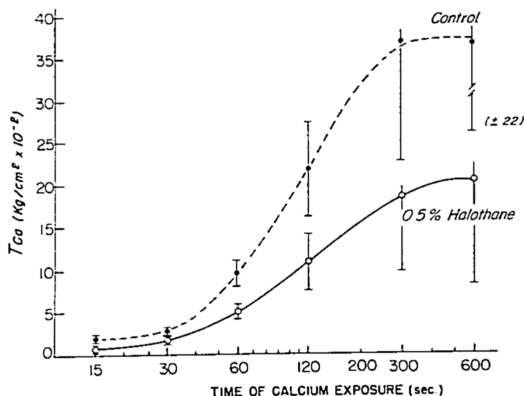

FIG. 2. Relationship between duration of exposure to calcium and mean initial tension response (T_{Ca}) in pregnant myometrial strips in absence (control) and presence of 0.5 per cent halothane. n = 6 in each group.

which does not cross the cell membrane, chelates all available calcium ions, whether they originated from within the muscle bundle or whether they were equipment contaminants.

These muscles remained unresponsive to K_2SO_4 for several hours, even in the absence of EGTA. Other smooth muscles under similar conditions retain only 20 per cent of their total intracellular calcium.[6] This suggests that in a calcium-free medium, replacement of ionized calcium from residual stores does not occur to any significant extent.

Since these uterine muscles were unable to produce a recognizable mechanical response (at a recorder attenuation of 1 cm = 0.1 g) with calcium-free K_2SO_4, we interpreted this to mean that with solution S, intracellular stores of ionized calcium were so low as to be unable to provide any calcium to the myofilaments for contraction, and that the muscles were functionally calcium-free.

When introduced into the muscle bath, calcium first equilibrates with the extracellular space surrounding the muscle fibers. It then enters the muscle fibers along both concentration and electrical gradients. The amount of calcium that immediately becomes available to activate cross-bridges is reflected in muscle tension during this period.

In the pregnant muscles, after the first 30 seconds of exposure to calcium, tension, and therefore myoplasmic calcium, rose exponentially until saturation was approached after 300 seconds. The delay observed in the initial 30 seconds may have been associated with equilibration of the extracellular space.

The postpartum muscles responded to calcium in a similar manner. However, the significantly larger I_t after 120 seconds of exposure to calcium in the postpartum compared with the pregnant muscles could have been due to their longer initial lengths. Other possible explanations include an increased influx of calcium into the postpartum muscles or an altered distribution of the influxed calcium. Because of the absence of any response to K_2SO_4, the latter possibility would appear to be most likely.

Calcium-sequestering intracellular organelles, such as mitochondria and sarcoplasmic reticulum (SR), compete with the myofilaments for influxed calcium.[7] The calcium-buffering propensity of these structures determines the level of myoplasmic calcium. When the muscle is stimulated to contract, calcium is released from the SR and becomes available to promote actin–myosin interaction. The developed tension (T_K) produced in response to stimulation after a given period of exposure to calcium is therefore a reflection of the amount of calcium taken up by, and hence available for release from, the SR. The absence of calcium in the depolarizing solution removed any possibility that some portion of developed tension was

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due to influx of calcium during depolarization or contraction. Other investigators[8] have failed to demonstrate the existence of such a mechanism in myometrium in any case. The possibility that some portion of T_K is contributed by release of calcium from other intracellular binding sites *e.g.*, mitochondria, in response to depolarization cannot be excluded at this time.[7] However, the lack of response to depolarization of the postpartum muscles suggests that uptake of calcium by the SR is severely limited in these tissues. This finding may be related to intracellular autolysis, which is actively proceeding in these muscles.[9] It also suggests that any contribution of residual calcium in the extracellular space to T_K is negligible.

The exponential increases in T_K and I_2 throughout the exposure times studied reflect the very high affinity of pregnant myometrial SR for calcium. +dP/dt, however, increased exponentially only with exposures of 60 seconds or less, and thereafter became constant. This finding suggests that in the first 60 seconds of exposure to calcium, insufficient calcium is transported into the SR to produce maximal intensity of the active state on depolarization.[10–12] Maximal active-state intensity appears to have been attained for exposures longer than 60 seconds, and the increased T_K seen under these conditions could represent either a diminished rate of decay of active-state intensity or the introduction of a plateau phase.[11]

In the pregnant muscles, the large decreases in I_1 produced by 0.5 per cent halothane indicate reductions in myoplasmic calcium levels of about 50 per cent. This effect is independent of the time of exposure to calcium.

If a reduction in intracellular calcium concentration occurs, it must mean that the net effect of halothane is to weaken those forces acting to increase calcium levels (transmembrane influx of calcium) relative to those forces acting to reduce calcium levels (sequestration by organelles and binding to intracellular sites).

The reduction in I_1 could be explained by an increased uptake of calcium by SR or mitochondria. However, halothane causes increased release of calcium from SR[13] and decreased mitochondrial calcium binding[13,14] and would therefore tend to increase myo-

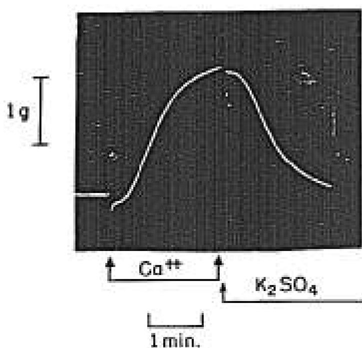

FIG. 3. The response of a postpartum strip of myometrium to a 120-sec exposure to Ca^{2+}, followed by depolarization with K_2SO_4 in the absence of Ca^{2+}. The K_2SO_4 depolarization did not induce any additional tension response.

plasmic calcium levels. In any case, the small reductions in T_K with halothane in the 60–600-second exposure groups indicate that at the concentration studied, this anesthetic does not cause a major effect on SR function. It therefore appears unlikely that the decrease in I_1 with halothane is due to an increased uptake of calcium by intracellular organelles. Increased binding of calcium to cell membranes, which occurs with other anesthetics, is not a feature of halothane action[15] and cannot be used to explain a decline in myoplasmic calcium levels.

A more likely explanation for the decline in I_1 is that halothane reduces calcium influx across the cell membrane. Because SR has a far greater affinity for calcium than the actomyosin complex, a decline in the total calcium influx would produce proportionately greater reductions in actomyosin calcium than in SR calcium. This would explain the greater effect observed in I_1 than in T_K, I_2 or +dP/dt.

The larger reductions in the latter modalities seen with halothane in the 15- and 30-second exposure groups suggest that decreased intracellular calcium may further diminish the submaximal active state that exists at these times.

In the postpartum muscles, reduction in Ca^{2+} influx probably occurs with halothane.

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However, the failure to develop tension in response to K_2SO_4, and the significantly greater tension development during the initial exposure to calcium (I_1) compared with the pregnant muscles, both suggest restriction of SR calcium-sequestering ability. This hypothesis is reinforced by the phenomenon of postpartum autolysis, which would be expected to reduce the quantity of contractile protein. Hence, a smaller T_K would be predicted for the postpartum muscles. Diminished uptake of calcium by the SR in the postpartum muscles will free a higher proportion of the influxed calcium for interactions with the contractile proteins, which would account for the increased I_1 in this group. Compared with the pregnant muscles, a smaller reduction in I_1 with halothane would therefore be anticipated, since any given reduction in calcium influx would not be compounded by the continued uptake of calcium by SR. These conclusions would not be altered even if increased I_1 in the postpartum muscles were a reflection of increased initial length.

Another explanation for the observed depressant effects of halothane could be that its action is upon the actomyosin–ATP complex. Halothane has been shown to exert a depressant effect on cardiac myofibrillar ATPase activity,[16] but little information is available on the effect of this anesthetic on the contractile proteins themselves.

In summary, myometrial strips obtained from pregnant or postpartum rats were rendered functionally calcium-free by exposure to a Ca^{2+}-free modified Krebs–bicarbonate solution containing EGTA. Both these tissues generated tension when subsequently exposed to Ca^{2+}, but the contractile response of the postpartum muscles was almost three times that of the pregnant muscles. Only the pregnant specimens were capable of responding to subsequent K_2SO_4 depolarization in the absence of Ca^{2+}. These observations suggest that the uptake of Ca^{2+} by sarcoplasmic reticulum is severely limited in postpartum muscles. Halothane (0.5 vol per cent) depressed the ability of both types of muscles to respond to Ca^{2+}, probably by reducing Ca^{2+} influx across the cell membrane. The smaller reduction in the tension response to Ca^{2+} with halothane found in the postpartum muscles is also consistent with a diminution of uptake of Ca^{2+} by the sarcoplasmic reticulum of these tissues.

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