Effect of intravenous and aerosol administration of 5-hydroxytryptamine on pulmonary function values in healthy calves

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SUMMARY

Effects of IV and aerosol administration of 5-hydroxytryptamine (5-HT) on ventilation, pulmonary mechanics values, pulmonary arterial pressure, and heart rate were investigated in healthy unsedated Friesian calves.

Minute volume increased significantly, mainly because of an increase in respiratory rate. Except for total pulmonary resistance after bolus injection, continuous administration of 5-HT given by either route caused significant alterations of lung dynamic compliance and total pulmonary resistance, the former decreasing to one-fifth of its baseline value and the latter increasing twofold. Pulmonary arterial pressure increased significantly, whatever the speed or route of administration. Administration of a bolus did not affect heart rate, whereas continuous IV administration of 5-HT as well by perfusion or by aerosol resulted in sustained tachycardia.

It was concluded that 5-HT induces reversible bronchoconstriction and pulmonary vasoconstriction in healthy unsedated calves, 5-HT-induced functional alterations depend on the speed of administration, and excess of 5-HT production or depression in uptake by the lungs during bovine respiratory tract diseases could contribute to pulmonary dysfunction.

Respiratory tract diseases have resulted in economic losses greater than all other diseases combined.[1] The knowledge of the actions and interactions of the autonomic and autacoid agents undoubtedly constitutes a basic requirement for a better understanding of the pathophysiologic processes in the development and treatment of respiratory tract diseases. In this context, the investigation of the reactivity of bovine airways to 5-hydroxytryptamine (5-HT) may be justified by 3 major arguments. First, 5-HT has already been shown to have many direct and indirect actions on smooth muscle and nervous structures at numerous levels and in many species.[2-4] Moreover, removal of 5-HT from the circulation constitutes one of the pulmonary capillary endothelium metabolic functions that is depressed early in the course of lung injury.[5,6] Accordingly, the depression of 5-HT uptake leads to increased concentrations in the circulation, which may contribute to the pathogenesis of lung dysfunction.[5] Second, 5-HT has been found in the bovine lung. Coupland and Heath[7] showed that bovine tissues contain at least 2 different types of mast cells, some containing predominantly histamine and others possessing monoamines, such as 5-HT and dopamine. Third, whereas bradykinin and histamine appear unlikely to be important in cattle,[8-11] other studies regarding the mediators involved in bovine anaphylaxis have led to conflicting results concerning 5-HT.[8,9,12,13]

In other investigations of the pulmonary effects of 5-HT on calf lungs, in vitro preparations were used[13,14] or respiratory rate and volumes were measured in vivo.[9,12] These latter measurements do not necessarily reflect development of abnormalities in lung function, whereas in vitro effects may not parallel in vivo responses. Furthermore, other experiments with 5-HT in cattle or sheep have been carried out with the animal under the influence of general anesthesia,[9,12] which may interfere with airway responses and may alter lung volumes.[15] For these reasons, the major objective of the investigation reported here was to characterize the effects of exogenously administered 5-HT on ventilation and pulmonary mechanics of healthy and unsedated calves. In addition, we monitored pulmonary arterial pressure and heart rate changes and determined whether the route and speed of administration of the mediator causes equal alterations of recorded values.

Materials and Methods

Animals—Six 7-month-old Friesian calves, weighing 210 ± 15 kg (mean ± SE), were used for this study. The calves were determined to be free from respiratory tract and cardiovascular disease by a thorough clinical examination the day of the study. The calves were placed in a wooden stanchion and were acclimated to our laboratory conditions for several weeks. Food was withheld 12 hours before each experiment. An air-conditioning system in the laboratory provided quasi-similar temperature and

Received for publication Dec 5, 1990.

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Supported by Belgian Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture, I.R.S.I.A., grant 5475A.

The authors thank Dr. Charles Michaux for statistical analysis of the data and J-F. Deneubourg and J-C. Leroy for technical assistance.

water vapor pressure characteristics of inspired air between experiments. Neither anesthesia nor sedation was given.

Measurement of variables—Respiratory airflow ($\dot{V}$) was measured by use of a heated pneumotachograph adapted to the head of the animal by a snug-fitting mask and coupled to a differential pressure transducer[a] with identical polyethylene catheter.[16] The $\dot{V}$ signal was subsequently integrated with respect to time to give tidal volume (V_t). Calibration procedures were performed before and after each experiment with a rotameter for the $\dot{V}$ and by forcing known volumes of air through the pneumotachograph for the volume. The air tightness of the mask had been checked previously by the closed-circuit helium-dilution method.[16] Esophageal pressure was measured by means of an esophageal balloon catheter made from a condom sealed over the end of a polyethylene catheter with a wide bore distal end in the part covered by the condom. The balloon tubing system was inflated with a minimum of air, within the range of high compliance of the balloon wall.[17] After lubrication, the catheter was introduced into the esophagus via a nostril and was positioned between the crossing point with the aorta and the caudal mediastinal lymph nodes according to the standardization procedure previously described for estimating pleural pressure in cattle.[17] The balloon catheter unit was then connected to a pressure transducer.[b] A hole made in the mask near the nostrils allowed the recording of airway opening pressure via a second similar catheter-transducer unit. All pressure transducers were calibrated against a water column and their responses were linear from −50 to 50 cm of H_2O. Frequency characteristics and phase compatibility of the recording systems (ie, pneumotachograph and pressure transducers) were satisfactory up to 6 Hz.[18] Transpulmonary pressure was electrically obtained by subtracting esophageal pressure from airway opening pressure and was used for the subsequent calculations. All signals (transpulmonary pressure, $\dot{V}$, V_t) were fed into a computer,[c] which derived mean pulmonary function values from measurements made on 15 regular, successive, and artifact-free respiratory cycles. Respiratory rate and V_t were measured by the software, whereas minute volume (V_E), dynamic lung compliance (C_{dyn}), and total lung resistance (R_L) were calculated by use of the method described by Rodarte and Rehder.[19] For the pulmonary function tests performed during 5-HT nebulization, the heated pneumotachograph was interposed between the mask and a nonrebreathing valve.[d] Two plastic tubes were connected to the inspiratory line of the valve via a "Y" tube. The first tube allowed the connection with a constant-flow nebulizer (0.4 ml of 5-HT solution/min) and the other was connected to the atmosphere. The diameter and length of this latter tube were carefully chosen to avoid an increase in flow resistance and leakage of nebulized 5-HT in the atmosphere during expirations. Expired air containing 5-HT was, in turn, captured in a meteorologic balloon. Pulmonary arterial pressure was obtained by using a fluid-filled catheter[e] connected to an extravascular pressure transducer[f] and an amplifier.[g] Position of the transducer was carefully adjusted to the level of the left atrium, that is, the scapulohumeral joint. The catheter was brought to its pulmonary arterial position by use of pressure monitoring via an introducer[h] placed in the right jugular vein. Calibrations were performed against a water column. An ECG was recorded by means of a single-channel electrocardiograph machine,[i] using a base-apex bipolar lead for heart rate calculation. A second catheter[j] was inserted into the left jugular vein for drug infusions 1 hour before investigation.[k]

5-Hydroxytryptamine challenges—5-Hydroxytryptamine hydrochloride[l] was used and the weights mentioned hereafter are expressed as active base of 5-HT. To make the calves familiar with the equipment, the mask and esophageal balloon were mounted at least 5 minutes before pulmonary function values were registered. The experiment was divided in 3 protocols, which were performed randomly at 2- or 3-day intervals (Table 1). The concentration of 5-HT into the nebulizer was selected for each calf to ensure quasi-similar delivery (0.05 mg/kg/min). In each study, control values were first measured before and during administration of saline solution. Subsequently, a challenge with 5-HT was performed during which R_L, C_{dyn}, V_t, respiratory rate, V_E, pulmonary arterial pressure and heart rate data were collected continuously from the beginning of administration to 20 minutes after.

Analysis of data—Pulmonary function values were derived from computations made on 15 successive regular respiratory cycles and are presented as mean ± SD before saline solution administration, during saline solution administration and 1, 2, 3, 4, 5, 10, 15, and 20 minutes after start of challenge exposure. A two-way analysis of variance was applied to the data. The differences between all pairs of means were tested by Duncan's multiple-range test.

Results

Clinical values—The experimental procedure was well tolerated by the 6 calves. Administration of saline solution by either route or speed did not induce any observable adverse effect. The response to 5-HT, consisting of congestion of conjunctiva, lacrimation, and tachypnea, was similar for any route or speed of administration. Apnea of 45 seconds' duration appeared 5 seconds after the 5-HT bolus injection. Also, 5 of the 6 calves defecated liquid feces 3 to 4 minutes after end of 5-HT perfusion.

[a] Validyne MP45, Gould, Wauthier-Braine, Belgium.
[b] Bentley Trantec M800, ACEC, Charleroi, Belgium.
[c] Heres, ACEC, Charleroi, Belgium.
[d] Hans-Rudolph, model 7200, Kansas City, Mo.
[e] Swan Ganz, 7F, Gould, Wauthier-Braine, Belgium.
[f] Statham, model P23D, Gould, Wauthier-Braine, Belgium.
[g] Sirecust, Siemens, Brussels, Belgium.
[h] Desilet 8F, Vygon, Brussels, Belgium.
[i] Cardiofax GEM, Nihon Kohden Corp, Tokyo, Japan.
[j] 16G, Vygon, Brussels, Belgium.
[k] Imed Ltd 960 volumetric infusion pump, San Diego, Calif.
[l] Sigma Chemical Co, St Louis, Mo.

Table 1—Description of the 5-hydroxytryptamine challenges performed in calves

Protocol	n	Route	Mode	Dosage	Duration
A	6	IV	Bolus	0.050 mg/kg	5 s
B	6	IV	Continuous	0.050 mg/kg·min	5 min
C	4	Aerosol	Continuous	0.050 mg/kg·min	5 min

Functional values—Intravenous and aerosol administration of saline solution had no significant effect on respiratory rate, V_t, V_E, C_{dyn}, R_L, pulmonary arterial pressure and heart rate, which averaged 32 ± 8 breaths/min (mean ± SD), 1.9 ± 0.8 L, 58.7 ± 17.2 L/min, 0.48 ± 0.08 L/cm of H_2O, 1.5 ± 0.8 cm H_2O·s/L, 29 ± 4.8 mm of Hg, and 87 ± 16 beats/min, respectively (Fig 1–3; Table 2). 5-Hydroxytryptamine administration induced significant changes of all the functional values. However, the pattern of these modifications was different, depending on the speed of administration. Continuous administrations of 5-HT (ie, protocols B and C) resulted in initial exponential-like modifications of most of the studied values, which were followed by plateaus. On the other hand, bolus administrations were characterized by strong, but short-lasting, alterations of functional values. The time course of functional changes was slightly different according to the route of administration. They appeared significantly earlier (R_L) and disappeared later (C_{dyn}) during the aerosol protocol than during perfusion. Except for C_{dyn} after aerosol, all values returned to baseline within 20 minutes after end of challenge exposure. Hyperventilation was always observed and was attributable to tachypnea, whereas V_t remained stable. However, R_L and heart rate were not modified by the bolus, except for a short-lasting period of severe bradycardia (42 ± 4 beats/min) occurring approximately 30 seconds after injection.

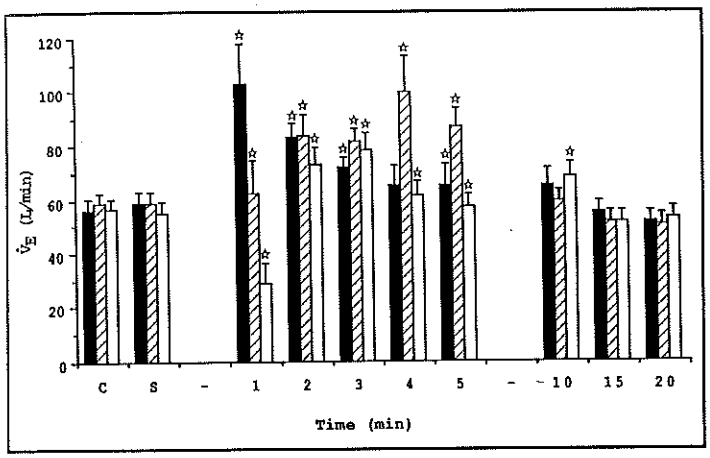

Figure 1—Effect of 5-hydroxytryptamine (5-HT) on minute ventilation ($\dot{V}E$) in healthy calves. All values are means ± SE. Measurements periods are displayed on the horizontal axis and include: control value, effect of saline solution, and 1, 2, 3, 4, 5, 10, 15, 20 minutes elapsed time after start of challenge. (■) 5-HT bolus injection, (▨) 5-HT perfusion, and (□) 5-HT aerosol. ☆ Significantly different from baseline at $P < 0.05$ level. † Significantly different from aerosol at $P < 0.05$ level.

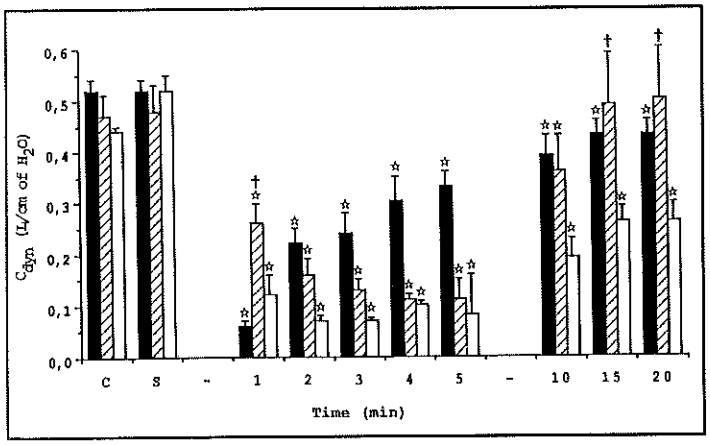

Figure 2—Effect of 5-HT on lung dynamic compliance (C_{dyn}) in healthy calves. *See* Figure 1 for key.

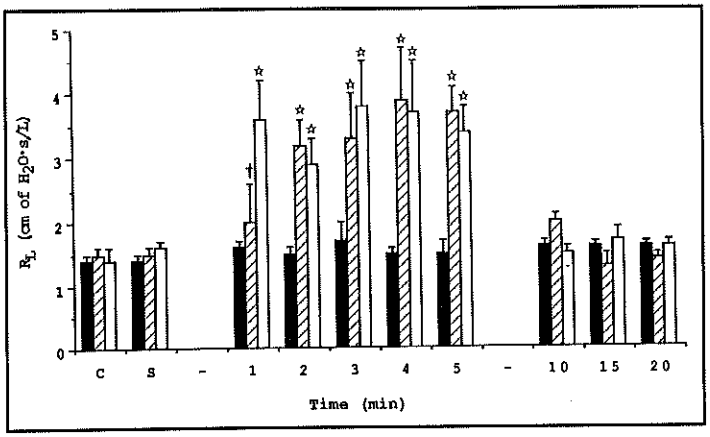

Figure 3—Effect of 5-HT on total pulmonary resistance (R_L) in healthy calves. *See* Figure 1 for key.

Discussion

Baseline values for ventilation and lung mechanics measured in this study did not differ from reference data for calves of the same breed and size (24.5 breaths/min, 1.89 L, 49.13 L/min, 0.44 L/cm of H_2O, and 1.4 cm of H_2O·s/L for respiratory rate, V_t, V_E, C_{dyn}, and R_L, respectively).[20] Resting pulmonary arterial pressure values in our conscious calves were in agreement with data given by Gross et al[21] (28 ± 4 [mean ± SE] mm of Hg) and Manohar et al[22] (34 ± 3 mm of Hg). Heart rates at rest were smaller, compared with those found by Gross et al (110 ± 10 beats/min), but confirmed those found by Manohar et al (90 ± 5 beats/min).

The observed increase in V_E, mainly attributable to tachypnea, is in accordance with previous investigations of the ventilatory effects of 5-HT on calves,[9] dogs, and cats.[23] The potent carotid body-stimulating effects of IV injection of 5-HT have been demonstrated in dogs and cats.[23] However, in other reports on 5-HT effects on the carotid bodies, 5-HT is excluded as an important neuroregulator in the mechanisms of chemoreception.[24] Furthermore, Aitken and Sanford,[9] in their study on the effects of mediators of anaphylaxis in calves, have precluded the possibility that 5-HT acts by stimulating chemoreflexes. Thus, although 5-HT appears to have an important effect on the regulation of ventilatory timing, the precise mechanism involved remains unknown. Furthermore, as suggested by Mills and Widdicombe,[25] there might also be species differences in the relative importance of different reaction pathways to 5-HT.

To our knowledge, the effects of 5-HT on pulmonary mechanic values of bovine lungs have not been previously determined. Experiments in vitro identified 5-HT activity on bovine airway or pulmonary vascular smooth muscle preparations.[14,26,27] The reversible decrease in C_{dyn} to approximately 20% of its baseline value observed here may have been induced by several factors. First, it is possible that a form of compliance frequency-dependency was measured. Indeed, a sinusoidally driven system of mul-

Table 2—Mean respiratory rate (RR), tidal volume (V_t), pulmonary arterial pressure (PAP) and heart rate (HR) changes induced by 5-hydroxytryptamine in healthy calves

Functional value		C	S	1	2	3	4	5	10	15	20
RR	A	32 ± 7^{a}	33 ± 7^{a}	$58 \pm 20^{a,b*}$	68 ± 15^{b}	63 ± 12^{b}	$49 \pm 12^{a,b}$	$49 \pm 12^{a,b}$	37 ± 7^{a}	32 ± 6^{a}	30 ± 6^{a}
(/min)	B	33 ± 7^{a}	33 ± 7^{a}	$38 \pm 10^{a,b}$	53 ± 12^{b}	53 ± 10^{b}	55 ± 7^{b}	53 ± 10^{b}	$45 \pm 7^{a,b}$	35 ± 7^{a}	32 ± 7^{a}
	C	30 ± 6^{a}	29 ± 6^{a}	29 ± 14^{a}	$56 \pm 22^{a,b}$	56 ± 12^{b}	56 ± 12^{b}	52 ± 14^{b}	36 ± 8^{a}	30 ± 8^{a}	30 ± 6^{a}
V_t	A	1.8 ± 0.5^{a}	1.9 ± 0.5^{a}	1.8 ± 0.2^{a}	1.3 ± 0.2^{b}	1.2 ± 0.2^{b}	1.3 ± 0.2^{b}	1.3 ± 0.2^{b}	1.6 ± 0.2^{a}	1.8 ± 0.5^{a}	1.8 ± 0.5^{a}
(L)	B	1.8 ± 0.5^{a}	1.9 ± 0.5^{a}	1.6 ± 0.2^{a}	1.6 ± 0.2^{a}	1.7 ± 0.5^{a}	1.8 ± 0.5^{a}	1.7 ± 0.2^{a}	1.6 ± 0.5^{a}	1.6 ± 0.5^{a}	1.7 ± 0.5^{a}
	C	1.9 ± 0.2^{a}	1.9 ± 0.2^{a}	1 ± 0.4^{b}	1.3 ± 0.4^{b}	1.4 ± 0.4^{b}	1.1 ± 0.4^{b}	1.1 ± 0.4^{b}	1.9 ± 0.4^{a}	1.7 ± 0.4^{a}	1.8 ± 0.4^{a}
PAP	A	$31 \pm 2.5^{c,d}$	$29.2 \pm 2.9^{c,d}$	43.9 ± 10^{a}	37.9 ± 4.7^{b}	37.6 ± 5.9^{b}	34.9 ± 5.9^{b}	35.1 ± 6.9^{b}	31.7 ± 8.3^{c}	$27.9 \pm 2.5^{c,d}$	27.9 ± 2.5^{d}
(torr)	B	30.2 ± 2.5^{c}	29 ± 2.9^{c}	29.1 ± 2.5^{c}	37.6 ± 4.2^{b}	41.1 ± 5.1^{a}	42.5 ± 5.1^{a}	43.3 ± 6.6^{a}	30.7 ± 6.6^{c}	27.6 ± 5.4^{c}	27.6 ± 5.4^{c}
	C	30.2 ± 2^{d}	29.7 ± 2^{d}	38.9 ± 3^{a}	39.7 ± 4^{a}	37.7 ± 3.2^{a}	40.1 ± 2.4^{a}	37.8 ± 3.4^{a}	$36.4 \pm 3.6^{a,b}$	$33.1 \pm 2^{b,c}$	$33.1 \pm 2^{c,d}$
HR	A	87 ± 10^{a}	81 ± 10^{a}	$71 \pm 25^{b*}$	$82 \pm 7^{a,b*}$	$76 \pm 12^{b*}$	$78 \pm 15^{b*}$	$73 \pm 7^{b*}$	$82 \pm 10^{a,b*}$	$87 \pm 12^{a,b}$	$89 \pm 12^{a,b}$
(/min)	B	93 ± 7^{c}	95 ± 10^{c}	110 ± 7^{b}	$119 \pm 12^{a,b}$	122 ± 10^{a}	$118 \pm 10^{a,b}$	$115 \pm 15^{a,b}$	96 ± 12^{c}	91 ± 13^{c}	91 ± 12^{c}
	C	90 ± 6^{b}	87 ± 6^{d}	101 ± 8^{a}	113 ± 12^{a}	113 ± 6^{a}	110 ± 10^{a}	110 ± 8^{a}	100 ± 12^{b}	88 ± 12^{b}	88 ± 12^{b}

* Significantly different from values recorded during continuous administrations (B and C, $P < 0.01$).
Measurement periods include: C = control value, S = effects of saline solution, and 1, 2, 3, 4, 5, 10, 15, and 20 minutes: elapsed time after start of challenge. Within each protocol, only those values with different superscripts are significantly different ($P < 0.05$).

tiple parallel pathways can be considered as a single pathway only if the time constants of the individual pathways are the same.[28] However, C_{dyn} was shown to increase with respiratory frequency in cattle.[29] This phenomenon was shown to be attributable to the length of the bovine extrathoracic airways, according to which inertia of the lungs and gas stream induces a significant overestimation of C_{dyn} in animals with a high respiratory rate, masking its tendency to decrease with respiratory rate during ventilatory asynchrony. On the other hand, one must consider that a significantly decreased C_{dyn} was still recorded when respiratory rate, V_t, and V_E had returned to control values (Table 2; Fig 1 and 2). Although the increase in respiratory rate could be one explanation of C_{dyn} changes recorded during 5-HT administration, it is probably not the most important factor. The decrease of C_{dyn} could also be attributable to constriction of the small airways.[30] Moreover, the decrease of C_{dyn} could have been associated with a diminution of lung volume by alveolar flooding or disturbances of elastic properties of the lungs by interstitial edema.[31] This hypothesis is strengthened by the observation that 5-HT has been shown to increase vascular permeability and protein extravasation in laboratory animals.[32] However, previous studies reported that pulmonary edema was absent from lungs of calves to which 5-HT had been administered.[9] Even lethal doses of 5-HT were found to induce only minimal patchy pulmonary congestion.[9] The rapid induction as well as the complete and fast reversibility of the C_{dyn} changes recorded in this study suggest that bronchoconstriction was the main pathophysiologic feature, but the presence of edema or important bronchial hypersecretion cannot be ruled out.

The twofold increase in R_L during 5-HT perfusion and aerosolization showed that there was also bronchoconstriction in the large airways. Indeed, Slocombe and Robinson[33] stated that small airways contribute only to a small fraction of the total resistance to $\dot{V}$ and Lekeux et al[34] further assumed that resistance of the peripheral airways accounts for only 10 to 20% of R_L in Friesian calves. Thus, the simultaneous decrease of C_{dyn} and increase in R_L to, respectively, one-fifth and twice their baseline value could result from a narrowing of central and peripheral airways, which is probably caused by diffuse bronchoconstriction. These findings are consistent with those of in vitro studies in which it was shown that 5-HT stimulates contraction of isolated bovine trachealis, bronchial, and bronchiolar muscles as it does in other mammalian species.[14] The healthy calf lung response to 5-HT administration is similar to those in healthy rats,[35] mice,[36] cats and dogs.[4] In contrast with continuous administration, the bolus injection did not increase R_L.

We observed 2 opposed effects of 5-HT on heart rate, depending on the speed of drug administration. First, the IV bolus did not affect heart rate, except for a short-lasting episode of bradycardia immediately after administration. Second, continuous administration, as well by perfusion as by aerosol, resulted in sustained tachycardia (Table 2). Such conflicting effects on the heart have been described.[37,38] They could be related to the wide spectrum of pathways through which 5-HT influences cardiac function. 5-Hydroxytryptamine has positive inotropic and chronotropic effects, which result from direct actions on cardiac tissue and indirect actions mediated by the release of norepinephrine from sympathetic nerve terminals.[37,38] Furthermore, these effects may be amplified or overshadowed by autonomic reflexes arising from the effect of 5-HT on systemic pressure. Unfortunately, we did not measure the arterial systemic pressure and cannot substantiate the assumption that tachycardia occurring during continuous administration was secondary to systemic hypotension primarily generated by 5-HT. Nevertheless, this pathophysiologic process has been described as well in calves as in guinea pigs.[9,39] Tachycardia occurring during perfusions and aerosols in this study may be explained by direct chronotropic effect and reflex catecholamine release, the relative importance of each process being undetermined. The immediate and short-lasting bradycardia observed after bolus may be explained, in turn, by the fact that 5-HT is known to have direct action on chemoreceptors in the coronary bed (Bezold-Jarisch reflex), because it may inhibit the sympathetic outflow and stimulate the activity of the cardiac vagus.[37,38] It must be emphasized that bradycardia occurred before the increase in pulmonary arterial pressure (vide infra), suggesting a direct action of 5-HT on the heart, rather than a hypertension-induced reflex effect. In contrast with continuous administrations, the bolus injections did not increase heart rate. This fact could be explained by the absence of direct chronotropic or indirect catecholamine-mediated effect on the heart.

Pulmonary arterial pressure increased significantly,

whatever the speed or route of administration. This result is consistent with results in earlier studies performed in vivo in calves,[9] dogs, and cats,[37,38] as with in vitro investigations that have demonstrated that 5-HT stimulates contraction of isolated bovine pulmonary arteries and veins.[9,13]

It is obvious that the total dose given as a bolus was one-fifth as large as the continuous infusion or inhaled dose (Table 1). It might appear that the speed of administration could not be discussed because the total dose given was not equal. However, the comparison of values recorded 1 minute after start of challenges A, B, and C is appropriate because the total dose administered is equal for the 3 protocols at this time. From a pharmacokinetic point of view, it can be predicted that the blood values would be significantly greater, but of shorter duration, for the bolus injection, compared with those for 1 minute of continuous administration. Hence, it could be predicted that responses would be greater in magnitude but shorter in duration, for the bolus injections. This was true for V_E, C_{dyn}, and pulmonary arterial pressure, but not for R_L and heart rate, perhaps because duration of the drug's presence in the blood was too short to allow diffusion to receptor sites in the large airway smooth muscle. This conclusion seems to be corroborated by the observation that R_L changes were significatively delayed during perfusion, compared with aerosol (Fig 3). Therefore, it can be suggested that 5-HT receptor sites could be more rapidly reached from the airway lumen than from blood vessels. In turn, the absence of tachycardia could result because 5-HT was not in the blood long enough to allow its diffusion to receptor sites in the myocardium (direct chronotropic action) or to trigger a reflex catecholamine release attributable to systemic hypotension. Also, the decrease in C_{dyn} after bolus injections in the absence of R_L changes may have some importance. Indeed, many of the effects of 5-HT are known to be dose-dependent.[38] Hence, C_{dyn} could have been modified by 5-HT blood values keeping R_L unaltered. This hypothesis is consistent with our observation that C_{dyn} changes occurred significantly earlier than R_L changes during continuous perfusions (Fig 2 and 3). Therefore, it can be suggested from these data that affinity or concentration of 5-HT receptor sites could be higher in smooth muscle of peripheral airways than in smooth muscle of central airways.

5-Hydroxytryptamine is known to be removed from blood and accumulated in pulmonary endothelial cells by a carrier-mediated, saturable, and temperature-dependent transport process.[6] Unfortunately, the kinetic analysis of this mechanism, giving Michaelis constant or maximal velocity, has been performed, to our knowledge, only in isolated perfused rat[40,41] and rabbit[41-43] lungs. However, other ways of expressing the extent of this process are by the percentage of extraction when the outflow concentration of 5-HT is related to its inflow concentration. From this kind of approach made in vivo in dogs, it was concluded that little or no 5-HT survives a single passage through the pulmonary circulation (up to 98% removed), suggesting a protective mechanism that prevents the amine from reaching the arterial circulation where it may have substantial cardiovascular effects.[43] Furthermore, radioactive techniques have shown that 5-HT is specifically taken up into cells that do not contain monoamineoxydase.[43] Accordingly, it was suggested that 5-HT could be stored to be metabolized later at a slower rate. If storage is involved, it is possible that administration of large amounts of 5-HT temporarily exceeds its capacity, some 5-HT escaping in the systemic circulation. This hypothesis could explain why a dose ≤ 40 μg of 5-HT/kg has no effect, whereas a dose of 70 μg of 5-HT/kg is lethal in cattle.[9] In the study reported here, a dose of 50 μg of 5-HT/kg was administered for the bolus injection after a 1-minute infusion. At this time, the observation of a decrease in C_{dyn} without a concomitant increase in R_L, which could be functionally related to airway constriction primarily caused by changes in the peripheral airways (vide supra), is consistent with the hypothesis that the only tissues that can be reached by 5-HT are those perfused by the pulmonary circulation. On the other hand, changes in the conducting airways (bronchial circulation), and intestinal function occurred only when the administered dosage of 50 μg/kg was increased further (from the second to the fifth minute), suggesting that the maximal storage capacity was exceeded allowing 5-HT to escape.

Thus, pharmacokinetic features, 5-HT receptor site characteristics, and pulmonary endothelial 5-HT clearance function could account for the different spectrum of physiologic actions related to the speed of administration.

In all calves, C_{dyn} returned to baseline value more rapidly after perfusion than after aerosolization (Fig 2). This discrepancy in the time course of recovery between perfusion and aerosolization could reflect a lesser efficiency of the pulmonary endothelial cells for taking up and metabolizing 5-HT from airway surfaces than directly from blood. On the other hand, increases in R_L, pulmonary arterial pressure and heart rate were reversed more rapidly than the decrease in C_{dyn} after challenge exposure was stopped (Table 2; Fig 3). This can be explained by the fact that the lack of collateral ventilation and the limited interdependence between lobules in cattle could have delayed the recovery of C_{dyn} from the bronchoconstrictive process.

It was concluded that administration of exogenous 5-HT induces reversible bronchoconstriction and pulmonary vasoconstriction in healthy unsedated calves, 5-HT-induced functional alterations depend on the speed of administration, and excess of 5-HT production or depression of its uptake by the lungs during bovine respiratory tract diseases could contribute to pulmonary dysfunction.

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