Effects of morphine and naloxone on fetal heart rate and movement in the pig

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The role of the endogenous opioid system in the control of cardiovascular function and locomotion has been a subject of research in adults for many years (26, 27). In general a suppressive action on heart rate (22, 26) and stimulatory effects on locomotion (27) have been reported. By contrast, only a few fetal studies have focused on cardiovascular and behavioral effects of opioids and opioid antagonists. These studies are difficult to compare, and their results are rather controversial. For example, administration of opiate agonists to the fetal lamb increases FHR (36, 38), body and eye movements (39), and electrocortical and respiratory activities (6, 17, 18, 35) and disturbs sleep-wake organization (37). Interestingly, the administration of naloxone to fetal sheep caused an increase in FHR as well (1). Smotherman and Robinson (34) found that morphine increased fetal motility (arousal) in the rat, whereas naloxone had no effect.

To explore the involvement of the opioidergic system in the control of cardiovascular and kinetic mechanisms in the fetal pig, we characterized and quantified the effects of a nonspecific opioid-receptor agonist (morphine) and antagonist (naloxone) on basal FHR, FHR variation, and FM.

METHODS

Animals. Twenty-one German Landrace sows (11–24 mo old) were kept in individual pens under controlled environmental conditions (temperature 20–22°C; lights on from 0600 to 1800). They received a standard diet twice daily (at 0630 and 1130) and had access to water ad libitum. Food was withheld from 12 h before to 12 h after surgery. Between 90 and 104 days of gestation (median: 100 days; term in this breed = 113 ± 1 days), one fetus per sow was chronically catheterized (n = 21) and 11 of them were also instrumented with electocardiograph (ECG) electrodes.

Surgical procedures. Surgical procedures were followed as previously described (4). Sows were sedated with azaperone (2 mg/kg; Stresnil, Janssen) 30 min before the induction of general anesthesia by means of ketamine-hydrochloride (12 ml via an ear vein, ketamine; Atarost). A Silastic catheter...
was placed into the maternal external jugular vein and was only used for maintenance of anesthesia with ketamine hydrochloride. Lateral laparotomy was performed, and one fetal compartment of the uterus, just ventral to the incision, was exteriorized and opened. A Silastic catheter (Silastic Medical Grade, no. 602-155, 0.51 mm ID and 0.94 mm OD, Dow Corning, Midland, MI) was placed into the fetal jugular vein and tunneled to the neck of the fetus. In 11 fetuses in addition to the vascular catheter, ECG electrodes (silver bars soldered to copper wires) were placed subcutaneously on both sides of the thorax and fixed to the fetal skin. After intra-amniotic administration of 500 mg kanamycin (Albrecht, Aulendorf, Germany), the fetal membranes and uterine wall were closed with one suture and the uterus was placed back into the abdominal cavity. The fetal catheter and ECG wires were tunneled subcutaneously and exteriorized at the back of the sow. On the day of surgery and the 2 following days, all sows received a standard antibiotic therapy (2 x 10⁷ IU penicillin and 2.5 g dihydrostreptomycin im; Tardomyocel, Bayer, Munich, Germany). Fetuses and dams were allowed to recover for 48 h before the experiments were started. Fetal catheters were flushed daily with 1 ml of saline and filled with 0.6 ml of saline containing 50 IU heparin (Kettelhack Riker, Borken, Germany) to keep them patent.

**Experimental protocol.** Fetuses were randomly assigned to a morphine or naloxone treatment group. The days of gestation on which FHR and/or FM recordings were made in individual fetuses are presented in Table 1. FM and FHR could be recorded simultaneously (i.e., around the same injection) in case of an ECG-derived FHR signal, but, because of interference of the two ultrasound systems, FM and Doppler-FHR recordings had to be performed on separate occasions. Only three fetuses were assigned to the saline group because their FHR and FM data did not differ from control fetuses in previous studies (7, 8). All experiments were performed by a single investigator. He was seated beside the sow during monitoring and was not informed about the kind of treatment. To eliminate possible diurnal variations, all experiments started at about the same time of day (0800–0930). Recording of FHR or FM started 15 min before intravenous administration of a nonspecific opioid agonist (morphine), nonspecific opioid antagonist (naloxone), or saline, and the recording lasted for 60 min. Morphine hydrochloride and naloxone hydrochloride (Sigma Chemical, Munich, Germany; 1 mg per fetus, resulting in an approximate dose of 1 mg/kg, assuming a fetal body weight of 1 kg at the time of injections) were dissolved in 0.5 ml of saline. Pilot experiments with different doses (unpublished observations) revealed that 1 mg/kg is the lowest effective dose. To assess the physiological condition of the fetus, blood samples (1 ml) were withdrawn at the start of each recording session. Venous blood gases, pH, and hematocrit (Hct) were analyzed using the blood-gas system 280 (Bayer Vital, Geschäftsbereich Diagnostics, Fernwald, Germany), calibrated on the reference temperature of the sow on the day of experiment. Median (range) venous blood Po2, Pco2, pH, and Hct at the beginning of the experiments were 20.7 Torr (18.0–22.7 Torr), 45.9 Torr (44.3–50.3 Torr), 7.41 (7.38–7.42), and 25.9% (24.1–27.6%), respectively. These values are considered to be within the normal range (30).

**Recording and analysis of fetal heart rate.** Noninvasive (Doppler ultrasound) and invasive (ECG) FHR monitoring was performed as described previously (7). In short, the catheterized fetus was visualized and its heart localized by means of transabdominal ultrasonography (Scanner 200, Pie Medical, Maastricht, The Netherlands), using a 3.5-MHz linear-array back fat probe with a scanning field of 18 cm (width) by 16 cm (depth). Then, a 1.5-MHz Doppler transducer connected to a cardiograph (Meridian 800, Oxford Sonicaid, Abingdon, UK; paper speed 3 cm/min) was placed on the maternal abdominal wall over the fetal heart. In case of a fetus with ECG electrodes, the electrodes were connected to the same cardiograph. FHR was recorded using Doppler ultrasound if the ECG electrodes were nonfunctional. Once a good-quality FHR signal was obtained, a handheld computer (Psion Organizer LZ II, Psion PLC, London, UK) was programmed to acquire data for 60 min. Off-line, the stored data were fed into a personal computer running a software package developed for human FHR analysis (System 8002, Oxford Sonicaid, Abingdon, UK), with which we encountered no problems to analyze heart rate in the fetal pig. Numerical FHR analysis included calculation of basal FHR (in beats/min), long-term variation (LTV; in ms), and short-term variation (STV; in ms). LTV was calculated as the average of 1-min pulse interval differences (mean minute range), whereas STV is the average of 1/16th-min pulse-interval differences (9).

The 1-h recordings were divided into four periods of 15-min (1 period before and 3 periods after drug administration), and each period was analyzed separately. During the Doppler-FHR recordings, FMs felt by the observer’s hand and movements of the sow were encoded with an event marker on the paper tracing, but they were not analyzed afterward.

**Recording and analysis of FM.** FM recording and analysis were performed as described previously (8). In short, the catheterized fetus was localized by means of transabdominal ultrasonography, using the same equipment as described for localization of the fetal heart. A longitudinal section of the fetus was maintained for 60 min continuously, and the images were stored on videotape. Off-line, the tapes were analyzed for the presence of movements of the whole body (GM),

**Table 1.** Distribution of fetal heart rate and/or movement recordings according to gestational age made in catheterized pig fetuses in each of three groups

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Fetus No. (Total n = 21)</th>
<th>Gestational Age at FHR Recording, days</th>
<th>Gestational Age at FM Recording, days</th>
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<tr>
<td><strong>Saline (n = 3)</strong></td>
<td>1</td>
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<tr>
<td><strong>Morphine (n = 9)</strong></td>
<td>4</td>
<td>102</td>
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<tr>
<td></td>
<td>5</td>
<td>106</td>
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<td>105, 107, 109, 111, 112, 114</td>
<td>112</td>
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n, No. of animals; FHR, fetal heart rate; FM, fetal movement.
isolated movements of the head (HM), isolated movements of a forelimb (LM), and rotation of the fetus along its longitudinal axis (Rot), using a specially designed software package (Poly 5, Inspector Research Systems, Amsterdam, The Netherlands). A single investigator analyzed the tapes and was not informed about the kind of treatment. The recordings were split into four periods of 15 min each (1 period before and 3 periods after drug administration). The incidence of each movement pattern was expressed as a percentage of observation time (15 min). The sum of the four percent incidences per 15 min was also calculated (total fetal activity (TFA)).

**Statistical analysis.** Because the data were not normally distributed they were expressed as median and range or interquartile range (IQR), and nonparametric tests were used. The Wilcoxon test was used to compare paired measurements, the Kruskal-Wallis test for comparison of the three treatment groups, and the Friedman test for repeated measurements within each group with the Neuman-Keuls method for multiple comparison. The relationship between two variables was studied with the Spearman test. Significant differences were assumed at the level of $P < 0.05$ (2-tailed). To achieve optimal visual presentation in Figs. 1 and 3, data were presented as means ± SE, but statistical significance was tested nonparametrically.

**RESULTS**

The median values for gestation length, litter size, and the proportion of stillborn piglets were 113 days (range 111–115 days), 11 piglets (range 9–14 piglets), and 12% (range 8–14%), respectively, and these values did not differ significantly between the three treatment groups. The percentage of stillborn piglets was relatively high (8% on average in this herd) because, in addition to the noninstrumented fetuses, the instrumented fetuses also were allowed to be born vaginally and several of them were born dead. Median birth weight of the operated fetuses was 1.1 kg (range 0.9–1.2 kg) and was within the normal range of all litters born.

**Effects of morphine and naloxone on FHR.** A total of 29 1-h FHR recordings was obtained from 15 fetuses and used for analysis (Table 1). The quality of these recordings varied widely among the fetuses. Whenever an ECG signal was recorded ($n = 10$), signal loss (SL; percentage of recording time) was <0.5%, whereas the median SL was 45% (range 4–74%) for the Doppler ultrasound recordings ($n = 20$). Maternal movements and FMs were the major reasons for SL.

During the control period (−15–0 min), there were no significant differences between the three treatment groups for any of the FHR parameters (Kruskal-Wallis test). Saline injection had no significant effect on FHR and its variation (Friedman test; Fig. 1). After morphine administration, FHR decreased dramatically ($P < 0.001$) within 55 s (median; IQR 30–80 s) and basal FHR remained reduced until 30 min after injection (Fig. 1), whereas both LTV ($P < 0.01$) and STV ($P < 0.05$) were increased for ~15 min compared with pretreatment values (Fig. 1). Naloxone administration resulted in a significant increase in FHR ($P < 0.001$) within 48 s (median; IQR 20–90 s), whereas no significant changes were observed in STV and LTV. The effect of naloxone on basal FHR remained present until 45 min after the injection. There was no significant relationship between the gestational age at recording and the fetal responses to either drug (i.e., change in FHR 0–15 min postinjection compared with control level; Spearman test). Examples of the rapid changes in the FHR pattern after administration of morphine and naloxone are presented in Fig. 2, A and B, respec-
Basal FHR was negatively correlated with LTV (Spearman rank correlation coefficient \( r_S = -0.36, n = 30 \) animals, \( P < 0.05 \)) and STV (\( r_S = -0.30 \), not significant) when all control periods were regarded. During the first 30 min after drug administration, however, only the correlation between basal FHR and LTV in the naloxone group was statistically significant (\( r_S = -0.40, n = 17, P < 0.05 \)).

Effects of morphine and naloxone on FM. A total of thirty-two 1-h recordings of FM was obtained from 16 fetuses and used for analysis (Table 1). The quality of these recordings was good, with SL (% of recording time not suitable for analysis) <15%. No significant differences were found among the three treatment groups during the control periods (Kruskal-Wallis test; Fig. 3). Saline injections caused no significant changes in any movement pattern (Friedman test). Morphine administration had no effect on GM, HM, and Rot, but it resulted in a dramatic increase in LMs within 115 s (median; IQR 99–123 s) after injection (Fig. 3). LMs were significantly increased until the end of observation (Fig. 3) and occurred in clusters of 45-s duration (median; IQR 24–65 s) alternating with epochs without LM (median duration 110 s; IQR 51–240 s, Fig. 4). The increase in LM resulted in a significant increase in TFA (Fig. 3). Administration of naloxone increased the incidence of GM (\( P < 0.05 \)), which occurred within 115 s (median; IQR 99–123 s) after injection (Fig. 3). Naloxone had no significant effect on either HM or LM. Fetal rotations were rare, and their incidence was not affected by any treatment (data not shown). There was no significant relationship between the gestational age at recording and the fetal responses to either drug (i.e., change in FM 0–15 min postinjection compared with control level; Spearman test).

Fig. 2. FHR patterns from 15 min before until 45 min after intravenous bolus administration of 1 mg morphine (A) or naloxone (B). Broken line, basal FHR as calculated by the computer. ↑, Time of injection.

Fig. 3. Changes in the incidences (% of time) of fetal body movements (GM), head movements (HM), forelimb movements (LM), and total fetal activity (TFA) recorded from 15 min before until 45 min after intravenous bolus administration (time = 0 min) of saline (0.5 ml; \( n = 8 \) animals), morphine (\( n = 8 \) animals), or naloxone (\( n = 16 \) animals) (both drugs 1 mg per fetus). Values are means ± SE; \( n \), no. of animals. Significance was tested for with the Friedman test. *\( P < 0.05 \). **\( P < 0.01 \).
Rapid tachycardia in the fetal sheep after administration (42). However, Adamson et al. (1) reported an induced tachycardia in a bell-shaped, dose-response manner (0.075–40 mg/h for 2–4 h) in the fetal sheep. In contrast to our observations in the pig, infusion of morphine (0.075–40 mg/h for 2–4 h) no increase in FHR was observed, suggesting that the tachycardiac response may be regulated via sympathetic activation. Administration of the opiate agonist U-50,488H to the fetal lamb increased the FHR immediately for a period of 15 min (36). This increase was subsequently followed by a prolonged decrease in FHR variability for up to 3 h. Pretreatment with naloxone blocked the tachycardia but not the decrease in FHR variation. All in all, these data indicate the involvement of both opioidergic and nonopioiergic mechanisms. The autonomic nervous system is especially well known to be a main regulator of fetal cardiovascular functions (3, 33). Among the findings mentioned above, only the results obtained by Adamson et al. (1) are in agreement with our results. It is, however, worth mentioning that in the fetal pig the δ-receptor is virtually absent until a few days after birth (20), whereas the δ-receptor is the major opioid receptor in the fetal sheep (40).

A strong negative relationship between basal FHR and LTV or STV has been found in the human fetus (23, 24). A negative correlation between basal FHR and LTV has also been described in the pig fetus (7) and was confirmed in the present study in the pretreatment control recordings. Interestingly, this negative relationship was still present after drug administration but only in the naloxone group. The increase in basal FHR seen after naloxone administration was not accompanied by a significant decrease in FHR variation. FHR possibly reaches the physiological limit after naloxone injection and therefore further changes in FHR variation can only be limited.

Morphine administration (400 μg/h via a mini-osmotic pump in the maternal flank) to fetal sheep induced rapid decrease in FHR, accompanied by increased LTV and STV. Naloxone administration (1 mg iv) caused an immediate increase in FHR without significant changes in LTV and STV. Available data on the effects of opioids and their antagonists on FHR in other species are inconsistent. Intramuscular administration of the opioid agonist pethidine (50 and 75 mg) (21) or fentanyl (31) to women during labor diminished FHR variation for 30 min. Naloxone administration to pregnant women (0.4 mg iv) resulted in an increase in the number of FHR accelerations (2). In contrast to our observations in the pig, infusion of morphine (0.075–40 mg/h for 2–4 h) in the fetal sheep induced tachycardia in a bell-shaped, dose-response manner (42). However, Adamson et al. (1) reported a rapid tachycardia in the fetal sheep after administration of naloxone (0.5 mg/kg as a bolus injection, followed by 1.3 mg·kg⁻¹·h⁻¹ continuous iv infusion), and these results are in accordance with the present study. In another fetal sheep study (19), administration of a μ-selective opioid peptide [tyrosine-d-arginine-phenylalanine-lysine-NH₂ (DALDA) 0.5 mg/kg iv] increased FHR gradually, reaching a peak between 50 and 70 min after administration and lasting for >120 min. When DALDA was administered together with naloxone (6 mg/h) or propranolol (β-adrenergic antagonist, 2 mg/h) no increase in FHR was observed, suggesting that the tachycardiac response may be regulated via sympathetic activation. Administration of the opiate agonist U-50,488H to the fetal lamb increased the FHR immediately for a period of 15 min (36). This increase was subsequently followed by a prolonged decrease in FHR variability for up to 3 h. Pretreatment with naloxone blocked the tachycardia but not the decrease in FHR variation. All in all, these data indicate the involvement of both opioidergic and nonopioiergic mechanisms. The autonomic nervous system is especially well known to be a main regulator of fetal cardiovascular functions (3, 33). Among the findings mentioned above, only the results obtained by Adamson et al. (1) are in agreement with our results. It is, however, worth mentioning that in the fetal pig the δ-receptor is virtually absent until a few days after birth (20), whereas the δ-receptor is the major opioid receptor in the fetal sheep (40).

**DISCUSSION**

The results demonstrate that intravenous administration of morphine and naloxone had differential effects on basal FHR, FHR variation, and FM during late gestation in the pig.

Fetal age at treatment ranged from 92 to 114 days. Although the development of fetal pigs during late gestation is rapid, we could not find any statistically significant age effect in our results. We therefore considered the differences in fetal age in our study to be of minor importance. Mean birth weight of the catheterized fetuses was 1.1 kg (range 0.9–1.2 kg). Therefore, it could only be concluded at birth that the dose of 1 mg per fetus had been actually higher in some fetuses but lower in others than the envisaged dose of 1 mg/kg body wt.

Intravenous administration of 1 mg of morphine to the pig fetus induced a rapid decrease in FHR, accompanied by increased LTV and STV. Naloxone administration (1 mg iv) caused an immediate increase in FHR without significant changes in LTV and STV. Available data on the effects of opioids and their antagonists on FHR in other species are inconsistent. Intramuscular administration of the opioid agonist pethidine (50 and 75 mg) (21) or fentanyl (31) to women during labor diminished FHR variation for ~30 min. Naloxone administration to pregnant women (0.4 mg iv) resulted in an increase in the number of FHR accelerations (2). In contrast to our observations in the pig, infusion of morphine (0.075–40 mg/h for 2–4 h) in the fetal sheep induced tachycardia in a bell-shaped, dose-response manner (42). However, Adamson et al. (1) reported a rapid tachycardia in the fetal sheep after administration of naloxone (0.5 mg/kg as a bolus injection, followed by 1.3 mg·kg⁻¹·h⁻¹ continuous iv infusion), and these results are in accordance with the present study. In another fetal sheep study (19), administration of a μ-selective opioid peptide [tyrosine-d-arginine-phenylalanine-lysine-NH₂ (DALDA) 0.5 mg/kg iv] increased FHR gradually, reaching a peak between 50 and 70 min after administration and lasting for >120 min. When DALDA was administered together with naloxone (6 mg/h) or propranolol (β-adrenergic antagonist, 2 mg/h) no increase in FHR was observed, suggesting that the tachycardiac response may be regulated via sympathetic activation. Administration of the opiate agonist U-50,488H to the fetal lamb increased the FHR immediately for a period of 15 min (36). This increase was subsequently followed by a prolonged decrease in FHR variability for up to 3 h. Pretreatment with naloxone blocked the tachycardia but not the decrease in FHR variation. All in all, these data indicate the involvement of both opioidergic and nonopioiergic mechanisms. The autonomic nervous system is especially well known to be a main regulator of fetal cardiovascular functions (3, 33). Among the findings mentioned above, only the results obtained by Adamson et al. (1) are in agreement with our results. It is, however, worth mentioning that in the fetal pig the δ-receptor is virtually absent until a few days after birth (20), whereas the δ-receptor is the major opioid receptor in the fetal sheep (40).

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Morphine administration (400 μg/h via a mini-osmotic pump in the maternal flank) to fetal sheep induced fetal arousal and behavioral state disturbance (37). Naloxone blocks or terminates fetal arousal in the sheep (18) but when administered to near-term pregnant women (0.4 mg iv) an increase in fetal body movements was seen (2). We found that intravenous administration of 1 mg of morphine to the pig fetus induced a rapid decrease in FHR, accompanied by increased LTV and STV. Naloxone administration (1 mg iv) caused an immediate increase in FHR without significant changes in LTV and STV. Available data on the effects of opioids and their antagonists on FHR in other species are inconsistent. Intramuscular administration of the opioid agonist pethidine (50 and 75 mg) (21) or fentanyl (31) to women during labor diminished FHR variation for ~30 min. Naloxone administration to pregnant women (0.4 mg iv) resulted in an increase in the number of FHR accelerations (2). In contrast to our observations in the pig, infusion of morphine (0.075–40 mg/h for 2–4 h) in the fetal sheep induced tachycardia in a bell-shaped, dose-response manner (42). However, Adamson et al. (1) reported a rapid tachycardia in the fetal sheep after administration of naloxone (0.5 mg/kg as a bolus injection, followed by 1.3 mg·kg⁻¹·h⁻¹ continuous iv infusion), and
that although morphine and naloxone induced an increase in FM, the stimulated movement patterns were different in nature. This suggests that morphine and naloxone act at different receptors in the nervous system controlling FM.

An interesting phenomenon was observed after morphine administration. LMs not only increased in frequency but also they occurred in clusters (Fig. 4). Apart from direct observation of these LMs during ultrasound scanning, this clustering was also subjectively felt by the hand of the observer during Doppler FHR monitoring. This type of movement occurred in a stereotyped manner (i.e., repetitively and with no obvious function) and is abnormal because it was never seen in the saline-treated fetuses or in other pig fetuses (8). To the best of our knowledge, this is the first time that a stereotyped behavior has been observed in a mammalian fetus.

The role of endogenous opioids in stereotyped behavior of adult sows has been extensively studied (32). When a sow is tethered she develops stereotyped behavior within 1 mo, which is probably regulated via controlling FHR and fetal kinetics. A more prolonged treatment with naloxone or more specific antagonists should disclose whether the previously observed decreases in FHR and FM occurring during late gestation (7, 8) can be influenced.

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