Effects of oral administration of caffeine on some physiological parameters and maternal behaviour of sows at farrowing

Effects of oral administration of caffeine on some physiological parameters and maternal behaviour of sows at farrowing

Paola Superchi, Roberta Saleri, Elena Farina, Valeria Cavalli, Enzo Riccardi, Alberto Sabbioni

PII: S0034-5288(16)30023-6
DOI: doi: 10.1016/j.rvsc.2016.01.023
Reference: YRVSC 3044

To appear in:

Received date: 31 August 2015
Revised date: 11 January 2016
Accepted date: 31 January 2016

Please cite this article as: Superchi, Paola, Saleri, Roberta, Farina, Elena, Cavalli, Valeria, Riccardi, Enzo, Sabbioni, Alberto, Effects of oral administration of caffeine on some physiological parameters and maternal behaviour of sows at farrowing, (2016), doi: 10.1016/j.rvsc.2016.01.023

EFFECTS OF ORAL ADMINISTRATION OF CAFFEINE ON SOME PHYSIOLOGICAL PARAMETERS AND MATERNAL BEHAVIOUR OF SOWS AT FARROWING

Paola Superchi, Roberta Saleri, Elena Farina, Valeria Cavalli, Enzo Riccardi, Alberto Sabbioni*

Department of Veterinary Science, University of Parma, Via del Taglio 10, 43126 Parma, Italy

*Corresponding author. Department of Veterinary Science, University of Parma, Via del Taglio 10, 43126 Parma, Italy. Tel.:+ 39 0521 032625; fax:+39 0521 032611.

E-mail address: alberto.sabbioni@unipr.it (A. Sabbioni).

SHORT COMMUNICATION

ABSTRACT

Caffeine has been demonstrated to have a protective effect on neonatal viability of piglets. In order to assess whether caffeine, administered to parturient sows, also affects maternal behaviour, respiratory rate, and dopamine, nitric oxide and serotonin plasma levels, 20 sows, with induced parturition, received orally 27 mg/kg of body weight of caffeine (T group; $n = 10$) or not (NT group; $n = 10$), on day 113 of gestation. Treatment did not affect the farrowing length. There were less stillborn piglets in T group than NT group (0.67 vs 2.44; $P < 0.05$), whereas no differences in dead piglets at 24 h from birth was observed. Caffeine did not affect physiological parameters of sows, as the behaviour score of sows laying on belly was reduced ($P < 0.05$). In conclusion, although the present study was carried out with a limited number of sows, administration of caffeine to parturient sows has the potential for reducing the number of stillborn.

Keywords: Swine; Caffeine; Farrowing sow; Behaviour; Stillbirth rate

Neonatal piglet mortality remains a major and multifactorial issue in pig farming (Decaluwé et al., 2014). Nutritional or management strategies that can increase piglets' neonatal survival have been developed (Herpin et al., 2001; De Vos et al., 2014; Theil et al., 2014). Treatment of neonatal asphyxia has involved the oral or subcutaneous use of caffeine in newborn infant (Schmidt et al., 2006; Orozco-Gregorio et al., 2011) and piglets (Orozco-Gregorio et al., 2010; 2012).

Caffeine, plays effects on various central and peripheral human tissues, arising primarily from antagonism of adenosine's actions via blockade of adenosine receptors (Magkos and Kavouras, 2005). By antagonizing the effects of adenosine in rats, caffeine can facilitate dopaminergic neurotransmission (Solinas et al., 2002). After oral administration in humans (Mose et al., 2008)

and pigs (Mazzoni et al., 2012), it is found in colostrum and breast milk. A study of Superchi et al. (2013) showed that oral administration of caffeine to sows at parturition contrasts the effects of perinatal hypoxia in piglets, which can improve their adaptation to extra-uterine environment and reduce ischemic brain damage. It is unknown if hyperactivity in the dopamine system induced by caffeine is associated with an increase in aggressive behaviour in sows, as observed in humans (Seo et al., 2008). Central and non-central effects of caffeine are mostly due to antagonism between adenosine and dopamine receptors, induced by caffeine (Solinas et al., 2002; Ferrè, 2008). Dopamine activity is mediated by nitric oxide (NO), whose synthesis is favoured by build-up of cyclic adenosine monophosphate induced by caffeine. Functional interactions between dopaminergic and serotonergic systems were also observed. In humans, the impairment of the serotonin system function can lead to deregulation of the dopamine system (Seo et al., 2008). In general, serotonin has an inhibitory action in the brain, contributing at prefrontal regulation of emotional responses by influencing inhibitory synaptic transmission and causing, among other consequences, anxiety (Yan, 2002).

Hyperactivity in the caffeine-induced dopamine system can affect the maternal behaviour in mice and rats; the impulsive aggressions, though stimulating effects, or depression would depend on the dose administered (Kayir and Uzbay, 2004; Solinas et al., 2005). In caffeine-treated sows, an increase in restlessness and aggressiveness, could interfere with the maternal performance at farrowing and be a direct (crushing) or indirect (delayed colostrum intake) cause of post-natal mortality of piglets (Edwards, 2002; Janczak et al., 2003).

In view of this, it was investigated whether caffeine administration, besides the positive effects on newborn piglet viability, has effects on physiological changes and on maternal behaviour of sows at farrowing.

All the experimental procedures were approved by the Ethics on Animal Experimentation Committee of Parma University.

Twenty Large White x Landrace crossbred sows were introduced to farrowing crates 4 days before they were due to farrowing (day 114 of gestation) and were assigned to two groups (n = 10/group), named T and NT. Mean (± sd) BW and parity order were, respectively, 238 ± 30 kg and 3.89 ± 1.32 in NT group and 224 ± 26 kg and 3.00 ± 0.85 in T group. Sows were fed 2.5 kg/day of a diet (15.36% crude protein; 9.57 MJ/kg NE, as fed basis), twice a day. On day 113 of gestation, T group received, once 27 mg/kg BW of caffeine (Sigma-Aldrich, St. Louis, Mo) mixed with 200 g of feed, before the morning meal (Mazzoni et al., 2012). The same amount of feed, without the addition of caffeine, was administered to NT group. Parturition was then induced by intramuscular injection of cloprostenol (0.175 mg/sow) (PGF VEYX ® forte, Veyx-Pharma GmbH, Söhreweg, Germany). At the day of farrowing, feed was withdrawn. The farrowing duration was calculated as the time interval between birth of the first and the last piglet, born alive or stillborn or mummified. The number of piglets, born alive, stillborn, mummified and dead within 24 h of life was registered. Data on postures and aberrant behaviours were recorded at the onset of labour and for 5 min every 20 min during the farrowing by the same observer by visual recording. The recorded postures were the following: standing (when all legs were perpendicular to the floor), lying on side (when one shoulder touching the floor), lying on belly (when the sternum or abdomen touched the floor), and sitting (when the rump was in contact with the floor with front legs extended perpendicular to the floor) (Jarvis et al., 2006). For each posture a score 0 (no position), 1 (posture lasting from 0 to 75 sec), 2 (76 - 150 sec), 3 (151 - 225 sec) or 4 (226 - 300 sec) was assigned. No recording of postural changes was done. The individual behaviours were averaged to a mean score/observation session/sow. The recorded aberrant behaviours (biting cage and piglets) were ranked, according to a score 0 (absence), 1 (1-25% of biting behaviour of the sow), 2 (26-50%), 3 (51-75%), 4 (>75%). Respiratory rate (breaths counted/min) was evaluated using the average of two measurements made for each session. Blood samples were collected at 113 days of gestation (before the morning meal) and one hour after the beginning of the farrowing. Plasma was obtained by centrifugation at 1800 x

g for 10 min at room temperature and then stored at -20°C until analysis. The analysed parameters were dopamine, NO and serotonin.

Dopamine was assessed by Dopamine ELISA (IBL International, Hamburg, Germany). The sensitivity was 0.4 pg/ml. The intra- and inter-assay coefficients were 5.3% and 8.7%, respectively. Nitric oxide was assessed by measuring nitrite levels in plasma by the microplate method (Ding et al., 1988). The absorbance was determined (VICTOR3, 1420 multilabel counter, PerkinElmer, Milano, Italy) using a 540 nm against 620 nm filter. The absorbance at 620 nm was subtracted to eliminate the yellow interference. The standard curve was performed using serial dilutions of sodium nitrite (50–0.39 μM; linear regression: $y= 0.0223x + 0.102$; $r = 0.99$). The interassay variability was less than 5%. Serotonin content was performed using a multispecies colorimetric competitive enzyme immunoassay (Serotonin EIA, Enzo Life Science, 3V Chimica S.r.l., Roma, Italy). The sensitivity of the method was 0.293 ng/ml and the variability coefficients within and among samples were 3.7% and 6.9%, respectively.

Data were analysed using a GLM procedure in SAS 9.4 (2012). The model included the group (two levels: T and NT) as a fixed factor. The basal values recorded before the caffeine administration and the number of total born piglets were used as a covariate. Behavioural data were analysed by the repeated measures procedure. Statistical significance was reached for $P < 0.05$. Differences among groups were considered significant if $P < 0.05$, and as a trend to significance when $0.05 \leq P < 0.10$. Caffeine mixed with the feed was quickly consumed by sows. Data on farrowing length (mean ± sd 249 ± 187 min) and litter performance are summarized in Table 1. Caffeine affected the number of stillborn piglets, which was 73% lower in T group than in NT ($P < 0.05$). At 24 h from birth, no differences in the number of dead piglets was observed ($P > 0.05$). Also score of physical activity of sows and aberrant maternal behaviour (mean number of scan behaviour/sow: 12) are reported in Table 1. All sows spent the greatest proportion of the observation periods in lying on side. The lying on belly was more prevalent in NT group ($P < 0.05$), while the sitting position tended to be higher in T group than in NT ($P < 0.10$). In both groups differences in aberrant behaviour were not

observed ($P > 0.05$). Treatment did not affect the respiratory rate and dopamine, NO, and serotonin plasma levels of sows ($P > 0.05$) (Table 2).

During farrowing, an increase of postural changes and activity of sows promotes the crushing of piglets (Edwards, 2002).

Furthermore, anxiety by mothers has been shown to have important effects on their offspring's later physiology and behaviour (Rutherford et al, 2014). In our study, farrowing was tackled mainly lying on side, according to sow physiology, and the postures that do not allow the piglets' full access to teats (standing, lying on belly, sitting) were not affected by caffeine administration.

As previously observed, stillborn piglets number in caffeine-treated sows decreases (Superchi et al., 2013). We can speculate that caffeine may reduce the risk of intra-partum mortality, acting on myometrial contractility in sows. Actually, the caffeine role in smooth muscle is inconsistent (Savineau and Mironneau, 1990, Tazzeo et al., 2012). In porcine myometrial cells, it was assumed the presence of different cell types that have different Ca2+ release mechanisms. This may imply various role for caffeine-sensitive Ca2+ stores in excitation-contraction coupling of smooth muscles (Zhuge and Hsu, 1995). Interestingly, caffeine has an indirect effect on uterine contraction, stimulating the synthesis and the release of PGF2α (Naderali and Poyser, 1994). Prostaglandin in turn, stimulating the formation of myometrial gap junction, that enables the rapid and efficient distribution of electrical impulses through the uterine muscle, promotes strong coordinated contractions, typical of active labor (Mitchell and Taggart, 2009). In fact, in our study, farrowing was induced by cloprostenol, that has a great affinity for PGF2α receptors and a long half life in the circulation (De Rensis et al., 2012). Thus, caffeine can be stepped in the synchronization of the contractions, physiologically important for maintaining the normal functions of hollow organs.

Although the present study was carried out with a limited number of sows, these findings allow us to emphasize that oral administration of 27 mg/kg BW of caffeine the day before the projected time of farrowing does not worsen the discomfort of parturient sows.

References

De Rensis, F., Saleri, R., Tummaruk, P., Techakumphu, M., Kirkwood, R.N., 2012. Prostaglandin F2a and control of reproduction in female swine: a review. Theriogenology 77, 1-11.

De Vos, M., Huygelen, V., Willemen, S., Fransen, E., Casteleyn, C., Van Cruchten, S., Michiels, J., Van Ginneken, C., 2014. Artificial rearing of piglets: effects on small intestinal morphology and digestion capacity. Livestock Science 159, 165-173.

Decaluwé, R., Maes, D., Wuyts, B., Cools, A., Piepers, S., Janssens, G.P.J., 2014. Piglets' colostrum intake associates with daily weight gain and survival until weaning. Livestock Science 162, 185-192.

Ding, A.H., Nathan, C.F., Stuehr, F., 1988. Release of reactive nitrogen intermediates and reactive oxygen intermediates from mouse peritoneal macrophages. Journal of Immunology 141, 2407-2412.

Edwards, S.A., 2002. Perinatal mortality in the pig: environmental or physiological solutions? Livestock Production Science 78, 3-12.

Ferré, S. 2008. An update on the mechanisms of the psychostimulant effects of caffeine. Journal of Neurochemistry 105, 1067-1079.

Herpin, P., Hulin, J.C., Le Dividich, J., Fillaut, M., 2001. Effect of oxygen inhalation at birth on the reduction of early postnatal mortality in pigs. Journal of Animal Science 79, 5-10.

Janczak, A.M., Pedersen, L.J., Rydhmer, L., Bakken, M., 2003. Relation between early fear- and anxiety-related behaviour and maternal ability in sows. Applied Animal Behaviour Science 82, 121-135.

Jarvis, S., Moinard, C., Robson, S.K., Baxter, E., Ormandy, E., Douglas, A.J., Seckl, J.R., Russell, J.A., Lawrence. A.B., 2006. Programming the offspring of the pig by prenatal social stress: neuroendocrine activity and behaviour. Hormones and Behavior 49, 68-80.

Kayir, H., Uzbay, I.T., 2004. Evidence for the role of nitric oxide in caffeine-induced locomotor activity in mice. Psychopharmacology 172, 11-15.

Magkos, F., Kavouras, S.A., 2005. Caffeine use in sports, pharmacokinetics in man, and cellular mechanisms of action. Critical Reviews in Food Science and Nutrition 45, 535-562.

Mazzoni, C., Sabbioni, A., Bertini, S., Menozzi, A., Piancastelli, C., Catelli, E., Zanardelli, P., Zambimi E.M., Saleri, R., Superchi, P., 2012. Estudio preliminary de la utilizacion de la cafeina en las cerdas en el momento del parto. Suis 90, 32-35.

Mitchell, B.F., Taggart, M.J., 2009. Are animal models relevant to key aspects of human parturition? American Journal of Physiology - Regulatory, Integrative and Comparative Physiology 297, R525-R545.

Mose, T., Kjaerstad, M.B., Nielsen, J.B., Edelfors, S., Knudsen, L.E., 2008. Placental passage of benzoic acid, caffeine, and glyphosate in an ex vivo human perfusion system. Journal of Toxicology and Environmental Health-part A 71, 984-991.

Naderali, E.K., Poyser, N.L., 1994. The effect of caffeine on prostaglandin output from the guinea-pig uterus. British Journal of Pharmacology 113, 103-110.

Orozco-Gregorio, H., Bonilla-Jaime, H., Mota-Rojas, D., Trujillo-Ortega, M.E., Roland-Santiago, P., Martinez-Rodriguez, R., Borderas-Tordesillas, F., Flores-Peinado, S., Mora-Medina, P., Ramírez-Necoechea, R., 2012. Effects of subcutaneous administration of caffeine on the physiometabolic profile of low-birthweight neonate piglets. Animal Production Science 52, 981-990.

Orozco-Gregorio, H., Mota-Rojas, D., Bonilla-Jaime, H., Trujillo-Ortega, M.E., Becerril-Herrera, M., Hernández-Gonzáles, R., Villanueva-Garcia, D., 2010. Effects of administration of caffeine on metabolic variables in neonatal pigs with peripartum asphyxia. American Journal of Veterinary Research 71, 1214-1219.

Orozco-Gregorio, H., Mota-Rojas, D., Villanueva, D., Bonilla-Jaime, H., Suarez-Bonilla, X., Torres-Gonzales, L., Bolaños, D., Hernández-Gonzáles, R., Martinez-Rodriguez, R., Trujillo-Ortega, M.E., 2011. Caffeine therapy for apnea of prematurity: pharmacological treatment. African Journal of Pharmacy and Pharmacology 5, 564-571.

Rutherford, K.M.D., Piastowska-Ciesielska, A., Donald, R.D., Robson, S.K., Ison, S.H., Jarvis, S., Brunton, P.J., Russell, J.A., Lawrence, A.B.,2014. Prenatal stress produces anxiety prone female offspring and impaired maternal behaviour in the domestic pig. Physiology and Behavior 129, 255-264

Savineau, J., Mironneau, J., 1990. Caffeine acting on pregnant rat myometrium: analysis of its relaxant action and its failure to release Ca^{2+} from intracellular stores. British Journal of Pharmacology 99, 261 – 266.

Statistical Analysis System (SAS), 2012. User's guide: statistics (version 9.4). SAS Institute Inc., Cary, NC, USA.

Schmidt, B., Roberts, R.S., Davis, P., Doyle, L.W., Barrington, K.J., Ohlsson, A., Solimano, A., Tin W., 2006. Caffeine therapy for apnea of prematurity. The New England Journal of Medicine 354, 2112-2121.

Seo, D.,. Patrick, C.J., Kennealy, P.J., 2008. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. Aggression and Violent Behavior 13, 383-395.

Solinas, M., Ferré, S., Antoniou, K., Quarta, D., Justinova, Z., Hockemeyer, J., Pappas, L.A., Segal, P.N., Wertheim, C., Müller, C.E., Goldberg, S.R., 2005. Involvement of adenosine A1 receptors in the discriminative-stimulus effects of caffeine in rats. Psychopharmacology 179, 576-586.

Solinas, M., Ferré, S., You, Z., Karcz-Kubicha, M., Popoli, P., Goldberg, S.R., 2002. Caffeine induces dopamine and glutamate release in the shell of the nucleus accumbens. The Journal of Neuroscience 22, 6321-6324.

Superchi, P., Mazzoni, C. Zanardelli, P. Piancastelli, C. Zambini, E.M., Beretti, V., Sabbioni, A., 2013. Effects of oral caffeine administration to sows with induced parturition on hypoxia in piglets. Livestock Science 157, 372-377.

Tazzeo, T., Bates, G., Roman, H.N., Lauzon, A., Khasnis, M.D., Eto, M., Janssen, L.J., 2012. Caffeine relaxes smooth muscle through actin depolymerization. American Journal of Physiology - Lung Cellular and Molecular Physiology 303, L334-L342.

Theil, P.K., Lauridsen, C., Quesnel H., 2014. Neonatal piglet survival: impact of sow nutrition around parturition on fetal glycogen deposition and production and composition of colostrum and transient milk. Animal 8, 1021-1030.

Yan, Z., 2002. Regulation of GABAergic inhibition by serotonin signaling in prefrontal cortex: molecular mechanisms and functional implications. Molecular Neurobiology 26, 203-216.

Zhuge, R., Hsu, W.H., 1995. The caffeine- and ryanodine-sensitive Ca^{++} store in porcine myometrial cells: its heterogeneity of all-or-none Ca^{++} release. The Journal of Pharmacology and Experimental Therapeutics 275, 1077-1083.

Acknowledgements

The authors would like to thank Dr. P. Benaglia (Mantova, Italy) for veterinary assistance and Bompieri farm (Pavone Mella Brescia, Italy) for logistic support.

Table 1 Least squares means of farrowing length, litter performance and active behaviour scores of parturient sows treated or not treated with caffeine

		Group[1]			
Item		NT	T	SEM[2]	*P*-value
Farrowing length	(min)	262.14	238.44	193.25	0.811
Litter size:					
- born[3]	n.	15.56	13.56	4.41	0.351
- born alive	n.	12.67	13.00	3.55	0.845
- stillborn	n.	2.44	0.67	1.80	0.042
- mummified	n	0.44	0.22	0.60	0.444
- dead within 24 h	n.	0.75	0.15	0.32	0.320
Active behaviour scores [4]:					
- standing		0.63	0.44	1.64	0.620
- lying on side		3.75	3.89	0.43	0.156
- lying on belly		0.88	0.00	0.12	0.003
- sitting		0.00	1.00	1.68	0.075
- biting cage		0.00	0.22	0.60	0.108
- biting piglets		0.00	0.11	0.46	0.289

[1] NT= sows treated with 0 g caffeine; T= sows treated with 27 mg/kg BW of caffeine on day 113 of gestation

[2] Pooled standard error of the mean.

[3] value used as a covariate for other litter size parameters

[4] the reported figures refer to scores obtained from a 0-to-4 scale (see text for details)

Table 2 Least squares means of respiratory rate and dopamine, nitric oxide, and serotonin plasma levels in parturient sows treated or not treated with caffeine

Item		Group[1] NT	T	SEM[2]	*P*-value
Respiratory rate	(breaths/min)	43.46	38.11	13.62	0.449
Dopamine	(pg/mL)	44.89	51.01	36.80	0.820
Nitric oxide	(µmol/L)	8.25	5.73	3.47	0.176
Serotonin	(ng/mL)	1.05	1.51	0.69	0.166

[1] NT= sows treated with 0 g caffeine; T= sows treated with 27 mg/kg BW of caffeine on day 113 of gestation

[2] Pooled standard error of the mean.

Highlights

- Caffeine orally administered to parturient sows;
- Caffeine does not cause behavioural changes in farrowing sows;
- Caffeine does not affect plasma levels of neurotransmitters of farrowing sows;
- Caffeine reduces stillbirth rate