Atti Accademia Nazionale dei Lincei

Classe Scienze Fisiche Matematiche Naturali

Rendiconti

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Foetal oxygen consumption and intrauterine implantation position in the rat

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti, Serie 8, Vol. **64** (1978), n.1, p. 89–94.

Accademia Nazionale dei Lincei

<http://www.bdim.eu/item?id=RLINA_1978_8_64_1_89_0>

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti, Accademia Nazionale dei Lincei, 1978.

SEZIONE III

(Botanica, zoologia, fisiologia e patologia)

Zoologia. — *Foetal oxygen consumption and intrauterine implantation position in the rat* (*). Nota di ROBERTO COLOMBO, presentata (**) dal Socio S. RANZI.

RIASSUNTO. — Sono state fatte prove riguardanti il consumo di ossigeno in feti di ratto albino, in relazione alla loro posizione intrauterina di impianto.

Quando il numero di impianti per ogni corno uterino è inferiore a 6 non sono state messe in evidenza differenze significative. Al contrario, quando il numero di feti, per ogni corno uterino, è maggiore di 6, si può osservare che i feti impiantati verso l'estremità tubale del corno uterino stesso (feti paraovarici) mostrano un consumo di ossigeno statisticamente più basso dei feti impiantati verso l'estremità vaginale (feti paravaginali).

Alla luce di precedenti esperienze è stato possibile proporre una spiegazione del fenomeno, mettendo in relazione cause ed effetti.

With the help of data available in the literature and the results obtained through laboratory tests, two zones could be determined in the rat uterus: a so-called *paraovarian zone* (corresponding to the tubal end of the uterine horn) presenting periembryonic environmental conditions rather adverse to embryonic development and the so-called *paravaginal zone* (corresponding to the vaginal end of the uterine horn), where embryos themselves find optimal development and growth conditions. In the paraovarian zone, foetuses show a strictly anaerobic metabolism with a poor energetic performance. In fact, they accumulate a high pyruvate rate under LDH inhibition by K-oxamate (R. Colombo and Giavini E., 1973) thus producing more lactate, under physiological conditions, as compared with those implanted in paravaginal positions (R. Colombo, Duzioni A. and Landoni C., 1977 in press); furthermore they present a feebler mitochondrial dehydrogenase activity than siblings implanted in the lower zones of the uterus (Colombo R. and Giavini E., 1975).

Placentae of paraovarian embryos show a very high affinity for lactate (Colombo R., 1977 in press) inasmuch as the corresponding foetuses produce a great amount of lactate (Colombo R., Duzioni A. and Landoni C., 1977 being published). It is, moreover, important to consider that the spontaneous foetal reabsorption rate is markedly higher towards the tubal end of the uterine horn than in the direction of its vaginal end (Colombo R. unpublished data)

(*) Lavoro eseguito nell'Istituto di Zoologia dell'Università di Milano.

(**) Nella seduta del 14 gennaio 1978.

and that at birth the paraovarian foetuses show a lower body weight than siblings implanted in the zones more favourable to development (Colombo R. unpublished data; McLaren A. and Michie D., 1960).

Correlating the above data with the fact that foetuses of the higher zones of the uterus are less sensitive to an experimental ischemia (Barr M. and Brent R.L., 1970) or to drastic maternal anoxies (Woollam D.H.M. and Millen J. W., 1962) it may be easily assumed that along the uterine horn there exists a utero-placental haematic irrigation gradient (i.e. pO_2) that from the high paravaginal district values sinks to the lower rates of the paraovarian district.

As the available amount of oxygen is presumably the conditioning factor for normal embryonic development, the intention was to test, with a new series of experiments, the oxygen consumption of rat foetuses with respect to the intrauterine implantation position.

For this series of experiments, 25 pregnant females of albino rat (Sprague Dawley stock) at the 15th day of gestation were used.

Once the animal was anaesthetized laparatomy was carried out, evidencing the pregnant uterus, and the foetuses present in each uterine horn were counted.

Foetuses of both uterine horns taken from the amnion were immediately immersed singly in a numbered basin of the Warburg apparatus, where there had been previously injected a solution containing:

0.154 M NaCl	100 parts
0.154 M KCl	4 parts
0.154 M $MgSO_4$	1 part
0.154 M KH_2PO_4	1 part
Glucose	0.1 %
0.25 M phosphate buffer, pH 7.4	21 parts

according to the method of Deotto (1942) and Umbreit, Burris and Stauffer (1949).

Foetuses were left intact as at the 15th day of gestation their dimensions do not markedly exceed the limit value of O_2 diffusion and, moreover, because we did not intend to determine absolute O_2 consumption values but rather the respiratory differences between different foetuses. The "direct method" for the measurement of the oxygen consumption has been used for this study according to the manometric technique suggested by O. Warburg Deotto R., 1942; Dixon M., 1943; Umbreit, W.W., Burris R.H. and Stauffer J. W., 1949).

The results obtained have been schematized in the following histograms.

In the first and second are recorded the oxygen consumptions for each single implantation position, for females respectively showing an implantation number exceeding 6 and minor/equal to 6, for a single uterine horn.

In the third and fourth histograms, the implantation positions have been no longer considered singly but in groups representing the three principal uterine districts: paraovarian, intermediate and paravaginal.

Histogram no. 3 refers to females showing more than 6 implantation sites per single uterine horn, while no. 4 refers to females with an implantation number minor/equal to 6.

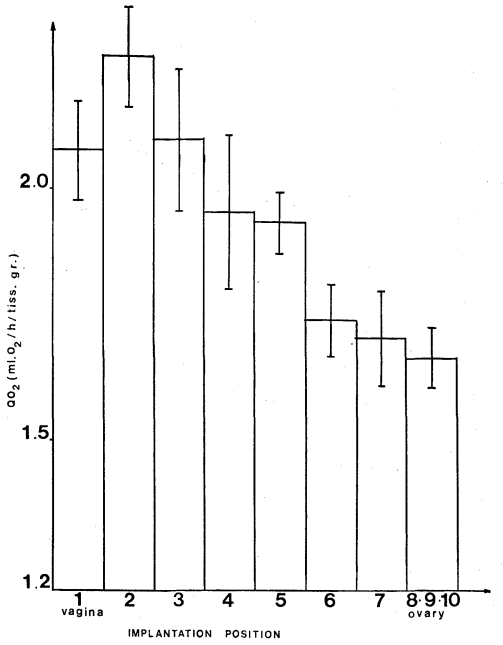

Fig. 1. – Data referring to foetuses from females with more than 6 implantation sites per single uterine horn.

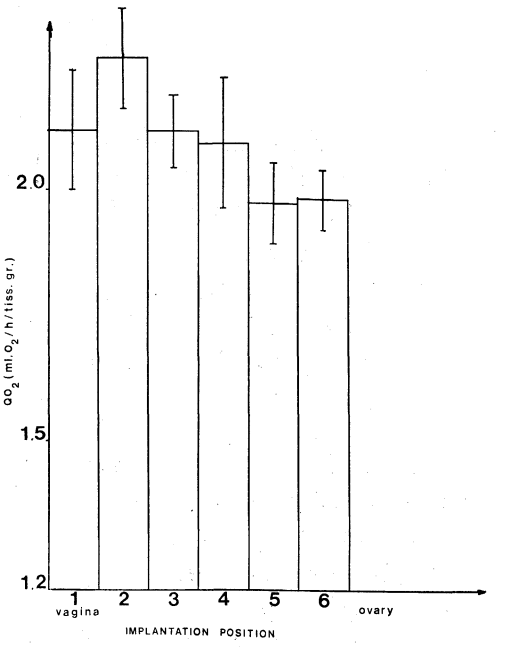

Fig. 2. – Data referring to foetuses from females with fewer than 6 implantation sites per single uterine horn.

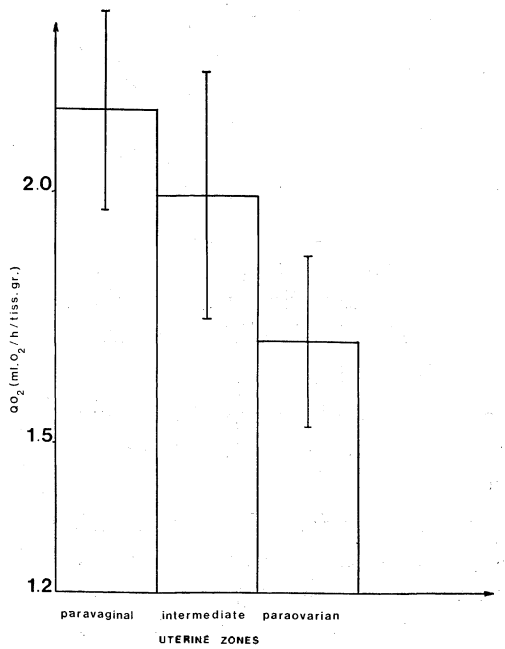

Fig. 3. – Data referring to foetuses from females with more than 6 implantation sites per single uterine horn.

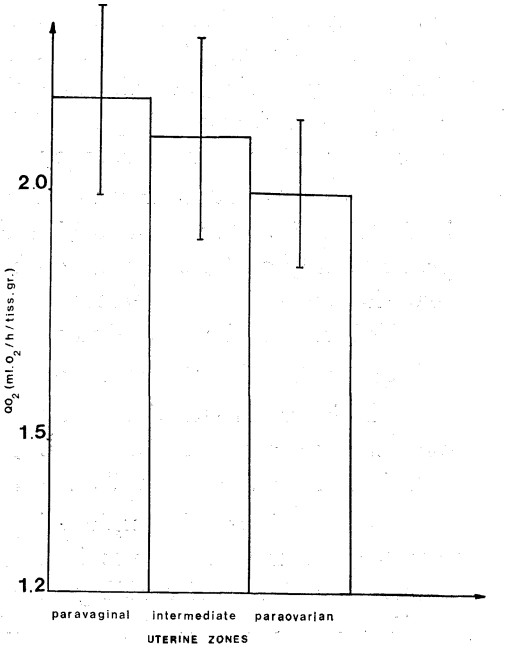

Fig. 4. – Data referring to foetuses from females with fewer than 6 implantation sites per single uterine horn.

Discussion

As is easily inferred from histograms no. 1 and no. 3, foetuses implanted in the uterine sites located near the vaginal end of the uterine horn show a higher QO_2 than siblings implanted in the paraovarian districts.

This fully agrees with data supplied by the literature or previously obtained in our laboratory.

In fact, in the light of results relevant to O_2 consumption, it clearly appears why the paravaginal foetuses, more than their paraovarian brothers, are affected by events such as experimental ischemia (Barr M. and Brent R. L., 1970) and maternal anoxia (Woollam D. H. M. and Millen J. W., 1962) whose ultimate result shows a drastic decrease of the O_2 supply. Further considerations, strictly connected with the above, concern the development of the mitochondrial apparatus.

In previous experiments, already mentioned in the introduction, we have evidenced in paravaginal foetuses a more intense activity in mitochondrial electron transport than in foetuses implanted in the paraovarian district (Colombo R. and Giavini E., 1975).

Furthermore, during a recent study, in foetuses implanted in the paravaginal area of the uterine horn we found a lower lactate/pyruvate ratio than that generally ascribed to foetuses implanted in the paraovarian district (Colombo R., Duzioni A. and Landoni C., 1977 in press); this would imply the fact that paravaginal foetuses are able to divert a part of the pyruvate produced through glycolysis into mitochondria, in the form of Acetyl-CoA and that, consequently, foetuses implanted in the most irrigated zone of the uterus have a better working Krebs cycle.

Comparing the latter data on the activity of the mitochondrial apparatus in foetuses from different uterine districts with the results obtained in the present study on O_2 consumption of the same foetuses, it might be assumed that the lower QO_2 in foetuses implanted in the paraovarian zone should be ascribed to the low development level of their mitochondrial apparatus.

Cause and effect should not, however, be confused.

The ischemia situation and consequently the foetal hypoxia in the paraovarian district for the foetuses implanted in this uterine area is pre-existing; therefore, all effects issue from this cause.

In our opinion, the explanation of the facts is the following: paraovarian foetuses, finding themselves in a low pO_2 development environment, have scarce possibilities of building an effective mitochondrial apparatus (Colombo R. and Giavini E., 1975; Colombo R., Duzioni A. and Landoni C., 1977 in press); alternatively, then, these foetuses elaborate a most efficient anaerobic glycolysis in order to produce the necessary energy for development (Colombo R. and Giavini E., 1973).

As a direct consequence of this, there is the low O_2 consumption rate of paraovarian foetuses and their scarce body weight at birth (Colombo R. unpublished data; McLaren A. and Michie D., 1960), all this accompanied by a high lactate production (Colombo R., Duzioni A. and Landoni C., 1977 in press).

In foetuses implanted in paravaginal zones of the uterus there is, evidently, the opposite situation.

From the above statements it is to be understood that we ascribe to O_2 an " inductive " action in respect to the foetal mitochondrial apparatus. As a last point, we have to focus our attention on the fact that significant differences in foetal O_2 consumption are verified only when foetal implantations, for a single uterine horn, exceed the number of 6 (compare histograms no. 1 and no. 2; no. 3 and no. 4).

A quite analogous fact had appeared in the work on placental metabolism of ^{14}C-lactate carried out in our laboratory (Colombo R., 1977 in press); also in these experiments, metabolic differences between placentae of the different uterine districts were evidenced only when for a single uterine horn the embryos numbered more than 6.

The hypothesis was then advanced that when the number of foetuses in the uterine horn was less than 6 at the moment of implantation, they could all be accepted in uterine areas provided with an adequate blood supply.

In the opposite instance i.e. when the number of embryos exceeded 6, some of these had no possibility of implanting in the uterine zones favourable to development and consequently they were occupying ischemic paraovarian zones, thus forcing anaerobic metabolic mechanisms in their aim to survive.

In the present state of experiments this explanation of the phaenomenon seems still to be the most satisfactory.

Acknowledgements. The author wishes to thank Dr. Claudia Landoni for her kind collaboration.

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