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Initial Permeability of the 19-Day Foetus to Nickel

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The administration of $^{63}NiCl_2$ to 19-day pregnant rats produced a limited transfer of nickel to the foetus. An experimental model based on the incubation of the conceptuses still connected to the maternal organism resulted in an appreciable net transfer of nickel through the amniotic membranes. The placenta retained a significant amount of radioactive nickel as did the lining of the uterine wall. The circulation of nickel through the foetus following the direction maternal blood → placenta → foetus → amniotic membranes → endometrium → maternal venous blood, is postulated. This transfer could provide an additional protection to placental barrier against metal toxicity.

Key words: Nickel toxicity, Placental transport, Fetal incubation.

Although nickel is a metal needed in very small amounts (13), it has profound toxic effects upon the mammal organism, affecting especially the glycemia and blood sugar utilization (1, 2). These effects are enhanced during pregnancy (7) due to a larger release of glucagon (6) following the nickel injection. Teratogenic effects of nickel in various species have been described (4, 5, 7). The actual nickel transfer across the placenta is, however, slight as determined both by direct measurements (5, 7-9, 14), and by autoradiographic tecniques with ^{63}Ni as a tracer (3, 10). Due to the short half life of nickel in the organism (9), the initial transfer of nickel across the placenta can be critical in the assessment of its fetotoxicity. The main objective of this research is to ascertain the actual direction of this metal transfer (if any) by using an experimental model based on incubation of conceptuses still connected to the maternal organism.

Materials and Methods

The experimental model used has been described previously (11). In short, nineteen-day pregnant rats were anesthetized with ether-air mixtures and then one uterine horn was exposed through laparatomy, the uterine wall was incised and ran-

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domly selected conceptus were exposed without affecting the placental implantation. The conceptus was washed with NaCl 0.9 % solution and then introduced in a beaker with 25 ml of phosphate buffered saline solution (37° C). Immediately afterwards, the rat was injected through the exposed femoral vein with 1.35 mBq of tracer free $^{63}NiCl_2$ (Amersham). Samples of maternal blood were removed from the tip of the cut tail. Samples of the saline solution were taken at intervals for ^{63}Ni estimation through liquid scintillation counting.

Foetuses were removed from the incubation medium at 1 or 5 minutes, and their placentae, whole foetus and amniotic membranes were weighed and then used for nickel radioactivity estimation. The reverse experiment (addition of the radioactive material to the saline solution to study the transfer to the foetus and maternal blood) was also carried out with a second series of pregnant rats. Tissue samples were digested with NCS^R (Amersham) prior the radioactivity measurements. All samples were corrected for quenching and the results expressed in becquerels.

Results and Discussion

The distribution of nickel in the foetus after maternal injection and the results of the reverse experiment are shown in table I and II. In the direct experiment, the radioactivity present in the placenta is considerable but lower than that in the maternal blood, remaining stabilized in the time span measured. This may be due to the large amount of blood trapped in this organ and suggests that the placenta does not concentrate nickel significantly in short term exposures. This is supported by the very short half life of this metal in the pregnant rat (5, 8) when administered in significant amounts. The presence of radioactivity in the foetus is low compared with that in the maternal blood and increased very slowly in the time studied. These findings confirm the suggestion that the placenta acts as an effective barrier for this metal in 19-day rat foetuses. However, the presence of a small yet significant amount of radioactivity in the amniotic membrane seems to point towards a transfer of radioactivity through the foetus towards the surrounding saline solution, which also showed a significant rise in radioactivity after incubation.

These results agree with a model of transfer which suggest a circulation of water (11) and may be other molecules be-

Table I. *Nickel radioactivity transfer through the foetal unit after injection of the mother with 1.35 mBq of $^{63}NiCl_2$.*

Values are the mean ± s.e.m. of duplicate measurements of 4 different animals.

Space/sample	Units	Time after the injection 1 min	5 min
Maternal blood	kBq/ml	53.3±0.5	—
Placenta (each)	kBq/g	25.0±0.3	21.7±0.4
Foetus (each)	kBq/g	0.3±0.04	0.4±0.05
Foetal envelopes (each)	kBq/g	3.3±0.5	2.8±0.04
Saline solution (25 ml)	kBq/ml	0.05±0.01	0.3±0.04

Table II. *Nickel radioactivity transfer through the foetal unit after incubation of a single conceptus in 25 ml of saline solution containing 1.35 mBq of $^{63}NiCl_2$.*

Values are the mean + s.e.m. of duplicate measurements of 4 different animals. Foetal data refer to the conceptus incubated.

Space/sample	Units	Time of incubation 1 min	5 min
Saline solution (25 ml)	kBq/ml	54.0±4.1	—
Foetal envelope	kBq/g	—	4.16±0.04
Foetus	kBq/ml	—	0.11±0.02
Placenta	kBq/ml	—	0.51±0.04
Maternal blood	kBq/ml	0.16±0.02	0.17±0.08

tween mother and foetus in the following way: mother to placenta to foetus to amniotic membrane to the mother again (uterus and venous blood). These findings could explain the bleak outlines of foetuses found in autoradiographic studies of nickel distribution (3, 7, 10) and similarly found for cadmium (12). These autoradiographies showed a marked outline of the uterine epithelium in contact with the amniotic sac, and a higher ^{63}Ni deposition in the placenta compared with the low level of retention by the foetus.

The results obtained in the reverse experiment showed that a significant amount of metal can be taken up by the foetal membranes and, probably through the extraembrionic circulation, can be transported to the foetus, where a small retention would be produced and would end up in the placenta. Only a very small amount would be trasferred to the maternal blood, which suggests that the «placental barrier» is effective in both directions.

According to this model, the foetus would have an additional mechanism of protection against metal toxicity, once a small amount of metal had crossed the placental barrier. A lack of foetal retention would allow nickel to reach the foetal membranes, which might transfer it to the maternal circulation again.

Resumen

La administración de $^{63}NiCl_2$ a ratas gestantes de 19 días induce un transporte limitado de níquel al feto. En un modelo experimental consistente en la incubación de unidades placento-fetales ligados al organismo materno se detecta transporte de níquel a través de las membranas amnióticas. Tanto la placenta como el útero circundante retienen una cantidad significativa de níquel radioactivo. En función de los presentes resultados se propone una circulación siguiendo la dirección: sangre materna → placenta → feto → membrana amniótica → endometrio → sangre venosa materna. Este mecanismo de transporte puede suponer una protección adicional a la barrera placentaria contra la toxicidad de metales.

Palabras clave: Toxicidad de níquel, Transporte placentario, Incubación fetal.

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