

Original articles

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The effect of Th 1165a upon the reactivity of placental vessels in vitro

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Th 1165a* belongs to the series of sympaticomimetic drugs chemically derived from epinephrine and ephedrine, such as Isoxsuprin, Dilatol, Aludrin (Isoprenalin) or Alupent.

In comparison with the above mentioned preparations, Th 1165a has a **better stability, a longer time of action and next to no side effects.** Because of its **excellent tocolytic effect** it is used in obstetrics for suppression of premature uterine activity as well as in all cases where the intensive uterine activity threatens the life of mother or fetus, e. g. in cases of placenta praevia (MOSLER [11], BODEN and V. D. CRABEN [1], ŠTEMBERA [16, 17]).

Th 1165 influences not only the uterine muscle but also smooth muscles of other areas (trachea and bronchi). There is also a **close correlation between uterine activity and blood flow in the uteroplacental area** (BROTÁNEK et al. [4, 5]), which undoubtedly influences indirectly the **circulation in the fetoplacental unit.** Owing to this fact there are some changes in fetal heart rate during uterine contraction or during intrauterine fetal hypoxia. **We studied the effect of this preparation upon the smooth muscles of the placental vessels.**

1. Methods and material

We established a method for measuring of the reactivity of placental vessels according to changes of the resistance in the vascular bed of a

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Curriculum vitae

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She entered the Charles University in Prague, 1945 and was graduated in 1950. After four years in a provincial hospital, she joined the Institute for the Care of Mother and Child in 1954. In 1956 she got her diploma as a specialist in obstetrics and gynecology, in 1966 the diploma as a candidate of sciences. Her current interested is the reactivity of placental vessels in relation to the course of pregnancy and labor.



wedge cut from the placental margin. After having probed the chorial arteries a perfusion of KREBS-RINGER solution with pneumoxyde and heparine added at pH 7.4 was performed by means of a pulsatory pump with a steady flow of 5 ml/min. Changes in the resistance of the vascular bed were measured by means of a STATHAM electromanometer and registered on a EZ 2 linear electronic recorder (JUNGMANNOVÁ, MIKULÁŠ, BROTÁNEK and HODR [9]).

We have investigated 17 placentas originating from spontaneous deliveries after normal courses of pregnancy. The experiment was arranged as follows: After two doses of norepinephrine (0.1 ml of the solution containing 10^{-8} g of norepinephrine in 1 ml of solution) two doses of

oxytocin Spofa (0.1 ml of the solution containing 10^{-12} I. U. in 1 ml of solution) were administered. A perfusion of the preparation with KREBS-RINGER solution containing 0.08 mg of Th 1165a per 100 ml followed. After 15 minutes administration of norepinephrine and oxytocin in the same doses and concentrations was repeated. Then the preparation was perfused with KREBS-RINGER solution only and the administration of norepinephrine and oxytocin was repeated.

Changes in the resistance of the vasculat bed in the form of positive pressure waves were measured planimetrically. One method was used in all experiments and the results were compared with another method; the area of the pressure waves was expressed in mm^2 . The standard scale for the pressure axis was 0.5 torr/mm, and for the time axis 0.05 min/mm. The conversion coefficient is $0.025 \text{ torr} \times \text{min./mm}^2$. The average value of the first two reactions to norepinephrine was considered to be a 100% response. The pressure waves after oxytocine were expressed as percent of the response to norepinephrine.

Statistical evaluation was performed by means of STUDENT'S t-test considering the fact that we always found the normal distribution in analogous experiments. In addition we also performed the unparametrical WILCOXON'S test.

2. Results

The magnitude of the responses after administration of norepinephrine and oxytocin and their standard errors are shown in Figs. 1 and 2. It is obvious that the reaction to both administered materials decreased in the course of perfusion by a solution containing Th 1165a.

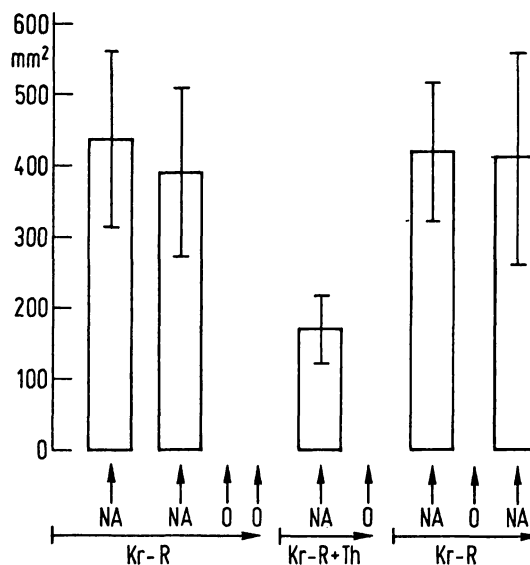


Fig. 1. Average reactions and their standard errors ($\pm s_{\bar{x}}$) after administration of norepinephrine before perfusion, during perfusion with Th 1165a and after perfusion as measured in square millimeters.

Kr.-R. = perfusion of KREBS-RINGER'S solution

NA = Norepinephrine

O = Oxytocin

Kr.-R. + Th = perfusion of KREBS-RINGER'S solution containing Th 1165a (0.08 mg of the drug per 100 ml of solution).

This decrease is statistically highly significant (according to WILCOXON'S test). In the course of the subsequent perfusion by KREBS-RINGER solution only the reactivity towards norepinephrine increases very much statistically, the decreased reactivity towards oxytocin is maintained (Tab. I and II).

3. Discussion

The results of our experiments show that the effect of Th 1165a on the smooth muscles of

Tab. I. The difference between the average reaction of placental vessels to norepinephrine before perfusion (1st dose = mean from the first two responses), in the course of perfusion by Th 1165a (2nd dose) and after perfusion (3rd and 4th dose) as measured in square millimeters.

Sequence of doses of norepinephrine	1.—2.	2.—3.	2.—4.	1.—3.	1.—4.	3.—4.
Number of cases	17	17	16	17	16	16
Average difference between average reaction	+232.35	-243.76	-235.56	-11.41	+10.89	+29.06
P (STUDENT'S t-test)	<0.05	<0.05				
P (WILCOXON'S test)	<0.01	<0.01	<0.01			

Tab. II. The difference between the average reaction of placental vessels to oxytocin before perfusion (1st and 2nd dose), in course of perfusion by Th 1165a (3rd dose) and after perfusion (4th dose) expressed in percent of reaction after norepinephrine.

Sequence of doses of oxytocine	1.—2.	1.—3.	2.—3.	3.—4.	2.—4.	1.—4.
Number of cases	15	16	15	17	15	16
Average difference between average reaction	+60.24	+137.29	+75.21	-40.35	+14.42	+87.11
P (STUDENT's t-text)		<0.01	<0.01			<0.05
P (WILCOXON's test)		<0.01	<0.01			<0.05

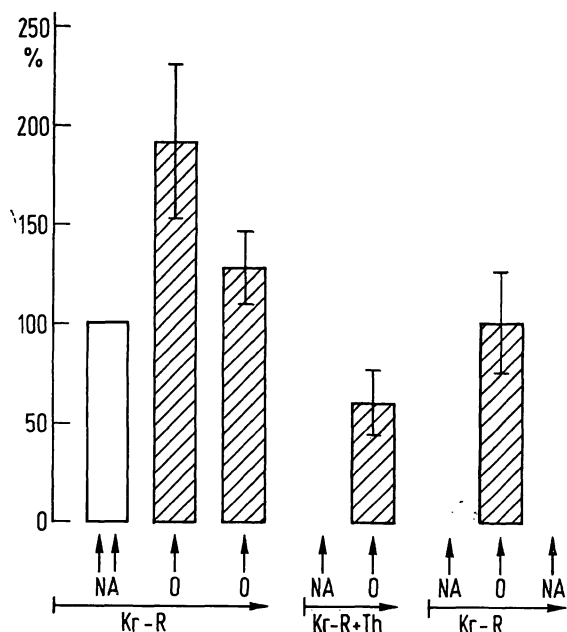


Fig. 2. Average reaction and their standard errors ($\pm s_x$) after administration of oxytocin before perfusion, during perfusion with Th 1165a and after perfusion expressed in percent of reaction after norepinephrine.

Kr.-R. = perfusion of KREBS-RINGER's solution

NA = Norepinephrine

O = Oxytocin

Kr.-R. + Th = perfusion of KREBS-RINGER's solution containing Th 1165a (0.08 mg of the drug per 100 ml of solution).

placental vessels, as demonstrated by the decreased reactivity towards oxytocine, is similar to the effect of Th 1165a upon the uterine muscle. BRUGGER and SALVA [6] have demonstrated on the isolated rat uterus that Th 1165a acts antagonistically upon the oxytocin-induced uterine activity. DE LA FUENTE, EZCURDIA, DE LA LASTRA and BOTIN [7] administered a Th 1165a infusion for 9 minutes

(0.08 mg/100 ml, 3 ml/1 min) to women in labor taking place in the 39th to 43rd week of pregnancy with a cervical dilatation of 6—9 cm. During the infusion spontaneous and oxytocin-induced uterine activity decreased substantially and was restituted within 20—30 minutes after cessation of the infusion. In our experiments we obtained similar results. Moreover we found that the reactivity of placental vessels towards norepinephrine was restituted more quickly than that towards oxytocin. The smooth muscles of placental and umbilical vessels differ from the other smooth muscles by their lack of innervation (SPIVACK [14], BOYD and HAMILTON [2]), though the innervation of the placental vessels of subhuman primates has been proved (FOX and JACOBSON [8]).

The nature of the reactivity of human placental vessels after the application of vasoactive substances allows to suppose the presence of both α and β receptors (MANCINI and GAUTIERI [10]). According to recent concept of the receptors in the form of enzymatic systems in cell membranes (WEIDINGER and WIEST [18]), the direct influence of Th 1165a upon the beta receptors and upon the cell membrane can be supposed also in placental vessels. This mechanism of action is very probable because Th 1165a influences the reactivity after oxytocin, which depolarises the cell membrane (BROTÁNEK [3]). It is still uncertain whether Th 1165a pervades the placental barrier and whether it is able to decrease the reactivity of placental vessels also in vivo. The passage of isoxsuprine is supposed (SHENKER [13], STANDER et al. [15], SANDLER et al. [12]). If Th 1165a also pervades the placental membrane, we can suppose its influence upon the circulation in the fetoplacental unit.

Summary

Th 1165a (Partusisten®, Boehringer) is being used for the suppression of uterine activity. Since Th 1165a influences also smooth muscles of other areas, we studied the effects of this preparation upon the smooth muscle of the placental vessels in vitro.

After having probed the chorial arteries we perfused a wedge cut from the placental margin by KREBS-RINGER solution at a steady flow of 5 ml/min. Changes in the resistance of the vascular bed were measured by means of a STATHAM electromanometer and graphically recorded. 17 placentas originating from spontaneous deliveries after normal courses of pregnancy were investigated. Reactions to a dose of norepinephrine and oxytocin were measured before, during and after perfusion containing Th 1165a (0.08 mg per 100 ml), and after rinsing the preparation.

Keywords: Perfusion, placenta, placental vessels-reactivity, Th 1165a.

Zusammenfassung

Der Einfluß von Th 1165a auf die Reaktionsfähigkeit der plazentaren Gefäße in vitro

Th 1165a (Partusisten®, Boehringer) wird zur Unterdrückung der Wehentätigkeit benutzt. Weil Th 1165a auch die glatte Muskulatur anderer Organsysteme beeinflusst, haben wir die Einwirkung dieses Präparates auf die Plazentargefäße in vitro studiert.

Nach Sondierung der chorialen Arterien haben wir einen Keilausschnitt aus dem Plazentarand mit KREBS-RINGER Lösung bei einer konstanten Geschwindigkeit von 5 ml/Min. perfundiert. Die Änderungen des Widerstandes der Blutgefäße nach der Applikation vasoaktiver Präparate wurden mit Hilfe des Elektromanometers Statham gemessen und graphisch registriert.

Untersucht wurden 17 Plazenten von Spontangeburt nach einem normalen Schwangerschaftsverlauf. Es wurden die Reaktionen auf Verabreichung von Noradrenalin und Oxytozin vor der Perfusion, während der Perfusion mit

Schlüsselwörter: Perfusion, Plazenta, Plazenta-Gefäße, Th 1165a.

Résumé

L'influence de la substance Th 1165a sur la réactivité des vaisseaux placentaires in vitro

La substance Th 1165a (Partusisten®, Boehringer) est employée pour réduire l'activité de l'utérus. Cette substance influençant aussi des muscles lisses dans d'autres parties du corps, nous avons étudié l'effet du Th 1165a sur la réactivité des vaisseaux placentaires in vitro.

Après cathétérisation de l'artère choriale, nous avons effectué une perfusion avec une solution KREBS-RINGER à un débit constant de 5 ml/min. sur un secteur du bord du placenta. Nous avons mesuré à l'aide d'un électromanomètre STATHAM et enregistré graphiquement les variations de résistance dans les vaisseaux placentaires après l'application des substances vasoactives.

The administration of Th 1165a significantly decreased the reactivity of placental vessels towards norepinephrine and oxytocin (Fig. 1 and 2). The reactivity of placental vessels towards norepinephrine was restituted more quickly than that towards oxytocin (Tab. I, II).

The results of our experiments show that the effect of Th 1165a on the smooth muscles of placental vessels in vitro is similar to that upon the uterine muscle, that is the decreased reactivity of the vessels. It is still uncertain whether Th 1165a pervades the placental barrier and whether it is able to change the reactivity of placental vessels in vivo. If this were true, we could suppose its influence upon the blood flow in the fetoplacental unit.

beigegebenem Th 1165a (0,08 mg/100 ml), nach der Perfusion und nach der Spülung des Präparates gemessen. Die Verabreichung des Th 1165a in der Perfusionslösung verursachte eine signifikante Erniedrigung der Reaktivität der plazentaren Gefäße auf Noradrenalin und Oxytozin (Fig. 1—2). Die Reaktivität der plazentaren Gefäße auf Noradrenalin wurde schneller wiederhergestellt als diejenige auf Oxytozin (Tab. I, II).

Die Ergebnisse unserer Versuche zeigen, daß der Einfluß des Th 1165a auf die glatte Muskulatur der plazentaren Gefäße ähnlich dem auf die Gebärmuttermuskulatur ist, soweit es die verminderte Reaktionsfähigkeit der plazentaren Gefäße betrifft. Es bleibt noch unklar, ob Th 1165a die Plazentarschranke überwindet und ob es auch in vivo die Reaktionsfähigkeit der Plazentargefäße verändern kann. Falls dies zutrifft könnte man seinen Einfluß auf die Durchblutung in der fetoplazentaren Einheit voraussetzen.

Nous avons examiné 17 placentas provenant d'accouchements spontanés après grossesses normales; nous avons mesuré les réactions à l'administration de noradrénaline et d'oxytocine avant la perfusion, pendant la perfusion avec du Th 1165a (0,08 mg/100 ml), après la perfusion et après le lavage de la préparation.

L'administration de Th 1165a dans la solution de perfusions a réduit de façon significative la réactivité des vaisseaux placentaires à la noradrénaline et à l'oxytocine (Fig. 1, 2). La réactivité de ces vaisseaux s'est rétablie plus rapidement dans le cas la noradrénaline que dans celui de l'oxytocine (Tab. I, II).

Les résultats de nos expérimentations montrent que l'influence du Th 1165a sur les muscles lisses est

similaire à celle sur le muscle de l'utérus, c. à. d. la réactivité réduite des vaisseaux placentaires. On ne sait pas encore avec certitude si le Th 1165a traverse la membrane placentaire et s'il peut modifier la réactivité des

vaisseaux placentaires in vivo également. S'il en était ainsi, on pourrait supposer son influence sur la circulation foeto-placentaire.

Mots-clés: Perfusion, placenta, Th 1165a, vaisseaux placentaires (réactivité).

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