COMPARISON OF HORMONE TRANSFER TO PLEURAL AND SYNOVIAL EXUDATES

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Objectives. Local effects of hormones on immune and connective tissues could play some role in the development of local inflammation processes. The aim of this study was to investigate the levels of selected hormones in pleural exudates of patients with pleurisy and lung tumours, and compare these levels with hormone concentration in knee synovial fluid.

Subjects and Methods. Eleven patients with pleural exudate (mean age 62±3) and l9 subjects with rheumatoid arthritis (of the same mean age) participated in the observations. Plasma, pleural exudates and synovial fluid levels of cortisol, prolactin, aldosterone, testosterone, 17-β-estradiol, dehydroepiandrosterone, progesterone, insulin and C-peptide were determined by specific radioimmunoassay.

Results. It was noted that all estimated hormones are transferred into pleural exudates and synovial fluid. Higher levels of dehydroepiandrosterone and C-peptide were observed in pleural exudates as compared to plasma. The concentrations of testosterone, prolactin and estradiol in males were lower in exudates as compared to plasma. Mean levels of cortisol, aldosterone, progesterone and insulin in plasma were similar to these found in pleural exudates. The comparison of hormone levels in pleural exudates and synovial fluid showed that the levels of cortisol, progesterone and dehydroepiandrosterone tended to be higher in the exudates as compared to synovial fluid. However, the levels of insulin, testosterone and estradiol in exudates were lower than these in inflammatory synovial fluid from patients with rheumatoid arthritis.

Conclusions. This study showed the presence of hormones in pleural exudates. The differences in hormone concentrations in pleural exudates and synovial fluid were observed suggesting a specificity of hormone transfer from plasma to these exudates.

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Key words: Cortisol – Insulin – Sex hormones – Pleural exudates – Synovial fluid – Pleurisy – Rheumatoid arthritis

Besides the plasma, various contents of hormones were demonstrated in several body fluids such as saliva, tears, peritoneal and synovial fluid (HAECKEL and HANECKE 1993; LAWRENCE 2002). These hormones are required for the proper function of epithelial layer of those organs from which they are secreted (e.g. oral mucosa, cornea, synovial cells). It was repeatedly observed that several hormones (e.g. gonadal and adrenal steroids, peptide hormones and catecholamines) show stimulatory or inhibitory effects on immune system functions including the influence of these hormones on inflammatory response. These effects were documented, specifically, by the action of hormones on local productions of cytokines and on the functions of immune cells at the site of inflammatory processes (CASTAGNETTA et al. 1999; ELENKOV and CHROUSOS 2002; GUTIEREZ et al. 1994; HAMANO et al. 1998; IMRICH 2002; LI et al. 1993; MORISHITA et al. 1999). Therefore, the knowledge on the presence and on the local effects of hormones on immune and connective tissues seems to be of key significance with

respect to pathogenesis of local inflammation processes. The changes of the concentration of hormones in synovial fluid were described in patients with rheumatoid arthritis (Cutolo et al. 1992; Elenkov and Chrousos 2002; Cutolo et al. 2002; Rovensky et al. 2004; Rovensky et al. 2005). However, there is a limited information on the level of hormones in pleural exudates, especially in human subjects and also on the local effects of hormones on pleural membrane. It was demonstrated in experimental animals that both the glucocorticoids and insulin affect the development of carageenin induced pleural exudates in rats (Cuman et al. 2001). Prolactin, a potent immunomodulator, affects the production of tumor necrosis factor-alpha (TNF-α) and nitric oxide in neutrophils of inflammatory pleural exudates at carageenin induced pleurisy in the rats (Meli at al. 1997). In human subjects, it was observed that the changes of the production of thyroid hormone and gonadal steroids influence the volume of pleural exudates (Hsu et al. 1990, van de Vrie et al. 1997).

The aim of present study was to investigate whether there exists any transfer of hormones from plasma to pleural exudates and which is the level of hormones in pleural exudates in patients with pleurisy and lung tumors. To obtain the appropriate information whether there are some differences in the transfer of hormones into pleural exudates and other body fluids, the concentrations of hormones in pleural exudates were compared to these found in the synovial fluids of knee joints in patients with rheumatoid arthritis.

Subjects and Methods

Eleven patients with pleural exudates (PEXD group, 6 males and 5 females, mean age of 62±3, among them 4 with lung tumors and 7 with pleural inflammation participated in the observations. In the second series there were patients of the same age range, with rheumatoid arthritis, (RA group, 7 females, 12 males, mean age 60±2). All patients which were admitted either to the Department of Tuberculosis and Lung Diseases, Vysne Hagy (Slovakia) or to the National Institute for Rheumatic Diseases (Piestany, Slovakia) were informed about the purpose of the study and gave written informed consent. The Ethical Committee of the Institute approved this study. The patients underwent routine clinical and laboratory investigations. Laboratory data included also erythrocyte sedimentation rate as well as plasma and urine biochemistry. In clinical assessment, the duration and clinical activity of disease, X-ray stage, and therapy were recorded. Patients which had either hormonal therapy (androgen or estrogen), diabetes mellitus or endocrine disorders were excluded from the study. Pleural exudates (PEXD) and synovial fluid (SF) were analyzed by routine biochemical, hematological and cytological methods.

Blood samples for hormone assays were obtained after an overnight fast. Plasma was separated and frozen until the levels of hormones were determined. Pleural exudates were obtained by punction of pleural cavity. Synovial fluid was collected during therapeutic arthrocentesis of knee joints. After centrifugation of exudates the supernatants were kept frozen until hormone analysis was performed. The pleural exudates were classified according Kristufek (1996) and synovial fluid according to Rovensky and Lukac (1996). Concentrations of the following hormones were determined in plasma and in clear supernatant of exudates: cortisol, (CS), prolactin (PRL), aldosterone (ALD), testosterone (TE), 17-β-estradiol (ES), dehydroepiandrosterone (DHEA), progesterone (PRG), insulin (INS), and C-peptide. The concentrations of hormones were measured by using commercially produced radioimmunoassay kits (Immunotech, Marseille, France).

Results for each variable were tested for normality distribution using Kolmogorov-Smirnov method. Results not normally distributed were logarithmically transformed for statistical analysis. Simple linear regression analysis was performed to correlate hormone levels within plasma and pleural exudates. The differences between groups were analyzed by using unpaired Student´s t-test.

Results

Determinations of hormone levels in pleural exudates showed that all hormones under study are transferred into these exudates (Fig.1). Positive correlation between hormone levels in plasma and PEXD was observed for ES, PRG, TE, DHEA, PRL, and INS (Fig.1). However, no significant correlation between the levels in plasma and exudates were found for aldosterone, cortisol and C-peptide (Fig.1). In both genders the concentrations of ES were lower in the exudates that in plasma, while in males such case was true only for TE and PRL (Table 1).

Mean levels of CS, ALD, PRG and INS in exudates were not significantly different from those in plasma (Table 1) which was possibly due to wide variation of their concentrations in PEXD or plasma. Higher values of the ratio of C-peptide and DHEA concentra-

Table 1.
Hormone levels in plasma and pleural exudates from patients with pleurisy or lung tumors.

	PLASMA		*PLEURAL EXUDATE*	
	F	**M**	**F**	**M**
ES	74±18	75±10	22±4	28±1
TE	0,08±0,01	1,90±0,27	0,08±0,02	0,87±0,20§
DHEA	1,23±0,60	1,87±0,78	2,36±1,30	10,05±3,68§
CS	360±85	456±66	426±223	404±222
ALD	83±25	78±24	37±9	126±65
PRG	0,29±0,07	0,55±0,22	0,29±0,06	1,06±0,61
PRL	10,1±3,4	6,5±1,4	7,8±2,9	4,2±0,4§
INS	65±19	40±5	58±15	39±5
C-pept	703±118	527±162	1306±214	922±374

ES – 17-ß-estradiol, pg/ml, TE- testosterone ng/ml, DHEA – dehydroepiandrosterone ng/ml, PRG progesterone nmol/l, ALD aldosterone pg/ml, CS cortisol nmol/l, PRL – prolactin ng / ml, INS – insulin pmol/l, C-pept – C--peptide pmol/l. Means± SE, § – Plasma: Exudate $p < 0,05$

Table 2.
Hormone levels in pleural exudates (PEXD), in synovial fluid (SF) and in plasma of patients with pleurisy or lung tumors (PT) or with rheumatoid arthritis (RA).

	PEXD	*SF*	*PLASMA*	
	PT	RA	PT	RA
Number	**11**	**19**	**11**	**19**
ES	25±2	38±4 §	75±9	57±5
TEm	0,87±0,20	1,62±0,22 §	1,07±0,32	1,36±0,30
DHEA	6,3±2,4	1,1±0,3 §	1,58±0,49	1,19±0,26
CS	415±150	157±18 §	393±60	163±27 §
ALD	85±36	85±15	80±16	74±18
PRG	0,71±0,34	0,26±0,03	0,42±0,12	0,26±0,04
PRL	5,8±1,4	6,1±0,8	8,8±1,7	7,4±1,1
INS	47±7	125±36 §	50±10	116±19 §
C-pept	1097±224	879±189	594±104	1280±193 §

ES– 17-ß-estradiol, pg / ml, TE- testosterone ng / ml, DHEA- dehydroepiandrosterone ng / ml, PRG progesterone nmol / l, ALD aldosterone pg/ml, CS cortisol nmol/l, PRL- prolactin in ng /ml, INS- insulin, pmol / l, C-pept – c-petide in pmol / l. Means± SE, § - PT to RA $p< 0,05$

tions in pleural exudates to their plasma levels were noted (Fig.1). However, no significant differences of hormone concentrations in pleural exudates were noted when the patients with lung tumors (non inflammatory exudates) were compared to patients with pleurisy (inflammatory exudates).

The comparison of mean hormonal levels in pleural exudates and in synovial fluids from knee joints showed that the levels of cortisol, progesterone and dehydroepiandrosterone in PEXD tended to be higher as compared to synovial fluid (Table 2). The levels of insulin, testosterone (in males) and estradiol were lower in PEXD as compared to inflammatory synovial fluid of patients with rheumatoid arthritis (Table 2, SF-RA). No significant differences in aldosterone, prolactin and C-peptide concentrations in PEXD and SF were noted (Table 2,). Besides cortisol, C-peptide and insulin, the concentrations of hormones in plasma of patients with pleural exudates and patients with rheumatoid arthritis were not significantly different (Table 2).

The determination of the ratios of plasma/synovial fluid or plasma/pleural exudates hormone contents

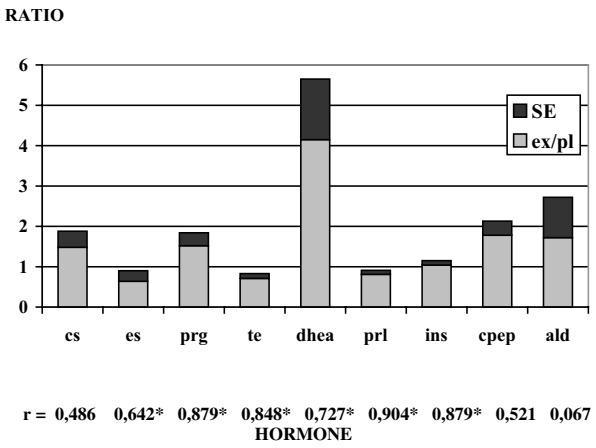

Figure 1 Ratio of hormone concentrations and coefficient of correlations of hormone levels in pleural exudate and in plasma.
Explanation of abbreviations: R = ratio, ex/pl = mean of ratios hormone concentration in pleural exudate to plasma hormone levels, SE = standard errors, cs = cortisol, es = 17-beta estradiol, prg = progesterone, te = testosterone, dhea = dehydroepiandrosterone, prl = prolactin, ins = insulin, cpep = c-peptide, ald = aldosterone.
r – coefficient of correlation, * – significant correlation of hormone levels in plasma and pleural exudate, p < 0,05.

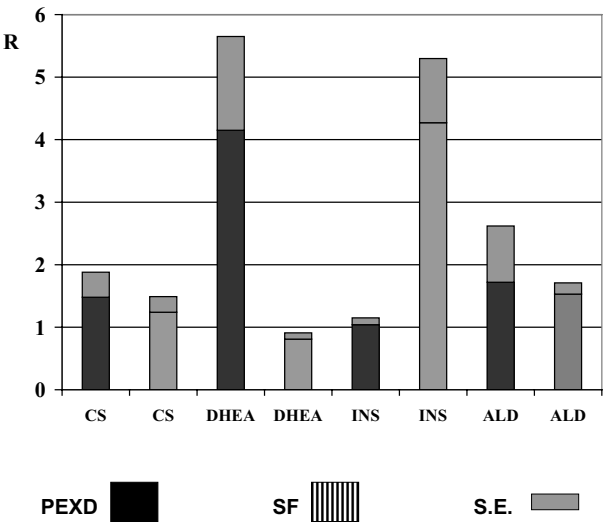

Figure 2 Ratio of hormone levels in pleural or synovial exudate to plasma concentrations.
Explanation of abbreviations: R = ratio, PEXD – pleural exudate, SF synovial fluid, S.E. – standard error. Means ± SE., Abbreviations of hormones see Figure 1.

showed further differences in hormone transfer from plasma to these fluids. The results demonstrated higher concentrations of insulin in synovial fluids as compared to plasma (Fig.2), but in the pleural exudates the levels of insulin were similar as in plasma. Lower levels of insulin in PEXD could be related to lower plasma insulin concentrations in patients with pleural exudates as compared to patients with rheumatoid arthritis (Table 2). The ratio of plasma/synovial fluid concentrations of DHEA was close to 1 (Fig.2); however, high values of the ratio of DHEA concentrations in pleural exudates to plasma levels were noted. No significant differences in the values of plasma/exudates ratios were noted for cortisol, aldosterone (Fig.2), estradiol, progesterone, testosterone, prolactin and C-peptide when their contents in pleural or synovial exudates to plasma concentrations were compared.

Discussion

It was suggested that the determination of hormones, antibodies, and certain drugs in body fluids could be explored in the early diagnosis of diseases, and also as a marker of monitoring the process of healing (Lawrence 2002). However, varying levels of hormones in body fluids like saliva, tears, synovial and peritoneal fluids were repeatedly demonstrated (Donnez et al., 1982, Robey et al., 1989, Kim Bjorklund et al., 1991, Haeckel and Hanecke. 1993, Manolopoulos et al., 2001, Lawrence 2002). In the present study we have examined the levels of hormones in pleural exudates and we have demonstrated for the first time that there exists a transfer of several hormones to the exudates. Nevertheless, it is not clear yet whether these hormones present in pleural exudates are of some influence on pleural inflammation. However, it should be underlined that this status differs from that of hormones present in synovial fluid during rheumatoid inflammations, since the hormones in synovial fluid can virtualy affect the inflammatory process in knee joints. The comparison of hormone concentrations in SF and PEXD showed some differences in the hormone composition of these exudates. Insulin levels were not higher in PEXD as compared to insulin plasma concentration. However, SF/plasma ratio of insulin level was significantly increased in patients with rheumatoid arthritis. Significant augmentation of DHEA levels was noted in PEXD of men as compared to plasma, but no differences in DHEA concentrations in plasma and SF was noted. Further studies are needed to explain these differences in PEXD and SF hormone content. It is interesting to note that the values of ratios of ES to TE, ES to CS, and ES to DHEA in PEXD were similar to those in synovial fluids from non-inflammatory knee joints of

patients with osteoarthritis (data not shown). However, in synovial fluids from patients with rheumatoid arthritis the values of estrogen to androgen concentration ratio were elevated. This shows the importance of a higher estrogen levels in SF for local inflammation processes in rheumatoid arthritis (Rovensky et al. 2004).

Further investigations are necessary to explain the role of hormones in pleural exudates during inflammation process. It was shown that glucocorticoids in pharmacological concentrations reduced the volume of inflammatory exudates during carrageenin-induced pleurisy in rats (Sannomiya et al. 1985). On the contrary, the removal of adrenal glands supports the reduced inflammatory response (by carrageenin induced pleurisy) in type 2 diabetic rats (Cuman et al. 2001). These results suggest the possible local effect of glucocorticoids on inflammatory process in pleural cavity. However, in our observations no significant differences in cortisol levels in PEXD were noted in subjects with pleurisy and exudates from lung tumors.

It was repeatedly demonstrated that local manifestations of rheumatoid arthritis are significantly influenced by gonadal steroids affecting the production of cytokines (Danis et al., 1992, Li et al., 1993). Elevated 17β-estradiol levels and lower testosterone and DHEA concentrations in plasma and synovial fluid were reported in patients with rheumatoid arthritis (Cutolo et al. 1992, Masi et al. 1996). However, the role of steroids in pleural inflammation is not fully clarified. The studies of the effects of 17-β-estradiol and progesterone on pleural tissues showed that these hormones can induce an increase of transepitelial electrical resistance and thus alter the transepitelial permeability (Hatzoglou et al., 2002). Steroid effects on the production of pleural exudates may be accounted for by a rapid release of nitric oxide (NO) in pleura. Significant reduction of the volume and number of cells in pleural exudates was noted during carageenin induced experimental pleurisy after injection of an inhibitor of NO-synthase (Meli et al. 1997).

Higher concentrations of DHEA were noted in pleural exudates as related to plasma levels especially in men. This is a great difference from the synovial fluid, since the levels of DHEA in knee exudates were similar to plasma values in both group of patients with osteoarthritis and rheumatoid arthritis (Rovensky et al., 2005). It was reported that androgens (including DHEA) with their anti-inflammatory action, could play some role in autoimmune rheumatoid inflammation, but their influence on pleural inflammation was not clarified. It is possible that higher levels of DHEA in PEXD may result from slower conversion of this hormone to metabolically active form (Schmidt et al., 2000, Cutolo et al., 2004).

It has been observed that prolactin is a potent immunomodulator that exerts stimulatory effects on physiological responses of immune cells. Thus, prolactin modulates the expression of genes and the production of growth factors and cytokine receptors (Gutierez et al., 1994). It was observed that prolactin could influence the production of inflammatory exudates of carageenin-induced experimental pleurisy in the rats by modulation of nitric oxide and TNF-β production in the neutrophils of exudates (Meli et al., 1997). We have found similar levels of prolactin in plasma and pleural exudates; however, beside the levels also the bioactivity of prolactin could affect the inflammatory processes. Berczi et al. (1987) observed that the bioactivity of prolactin was significantly decreased in rheumatoid patients, when compared to values obtained in age and sex matched controls. In our observation the prolactin bioactivity was, however, not performed in pleural exudate.

The presence of aldosterone in pleural exudates was demonstrated for the first time in our observation. The levels of this hormone in pleural exudates were similar as compared to synovial fluid of patients with rheumatoid arthritis. There are only few observations of aldosterone effects on the inflammatory processes. It was noted that aldosterone shows a pro-inflammatory action in patients with chronic arthritis (Sun et al. 2002, Gerling et al. 2003, Bendtzen et al. 2003) The demonstration of increased levels of aldosterone in the plasma and synovial fluid in patients with rheumatoid arthritis in our previous observation (Rovensky et al. 2004) is in agreement with the pro-inflammatory action of aldosterone, and ~~it~~ this suggests a possible role of local aldosterone in the inflammation of synovial tissue. However, there are no data on the possible role of aldosterone in production of pleural exudates.

The role of insulin in the inflammatory process is still not clear. An enhanced susceptibility to infection is known to occur in poorly controlled diabetes (Otton et al. 2002). Diabetic rats with type 2 diabetes showed reduced inflammatory response to carrageenin induced pleurisy. It was interesting to note, that this reduction of pleural exudates in insulin resistant animals was partially corrected by removal of adrenal glands (Cuman et al. 2001). The lower inflammatory response to carrageenin in type 2 diabetic rats is probably a result of an impairment of elevation of permeability in pleura induced by serotonin or bradykin (Cuman et al. 2001). The changes in transepitelial permeability of pleural

membrane may be accounted for by the changes in nitric oxide production, which was observed after prolactin, 17â-estradiol and progesterone (Meli et al. 1997, Hatzgoglou et al. 2002). Therefore further investigations including determination of insulin effects on nitric oxide production in visceral and parietal pleura are necessary to explain the changes in response of diabetic animals to induction of pleural inflammation.

In conclusion, our study showed that besides the glucocorticoids, estrogens and androgens as well as INS, c-peptide, ALD, PRL are present in pleural exudates. The higher levels of DHEA were observed in pleural exudates as compared to those in plasma. The comparison of hormone concentrations in synovial fluid and pleural exudates showed some differences in the hormone spectrum of these exudates. The concentrations of cortisol, testosterone and DHEA were higher and those of insulin were lower in pleural exudates as compared to synovial fluid. Also the values of ratios of INS, and DHEA content in synovial fluid to plasma and the ratios of these hormone levels in pleural exudates to plasma were different suggesting some specificity in the hormone transfer from plasma to these body fluids.

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