5-Hydroxytryptamine Metabolism in Joint Diseases

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IGARI, T., TOBA, Y., OBARA, K. and Ono, S. 5-Hydroxytryptamine Metabo-
lism in Joint Diseases. Tohoku J. exp. Med., 1974, 112 (4), 355-359 —— Trypto-
phan metabolites through 5-hydroxytryptamine in the synovial fluid and blood of
patients with rheumatoid arthritis and those with osteoarthritis were investigated
in order to know the role of serotonin in the joint diseases. A metabolic map of
tryptophan in the synovial fluid was also made. There were no significant
differences in the levels of 5-hydroxytryptamine and 5-hydroxyindole acetic acid
in the synovial fluid between rheumatoid arthritis and osteoarthritis, but the
activity of monoamine oxidase in the synovial fluid was higher in osteoarthritis
than in rheumatoid arthritis.——— synovial fluid; serotonin; monoamine oxidase

We reported previously on the tryptophan and its metabolites in the synovial
fluid in joint diseases, and a metabolic map via kynurenine pathway was made
(Knox 1953; Igari et al. 1969; Tsuchizawa 1969). Since then the present authors
have studied the metabolic pathway from tryptophan to 5-hydroxyindole acetic acid
(5-HIAA) through 5-hydroxytryptamine (5-HT=serotonin) in the synovial fluid,
blood and urine of patients with joint diseases (Fig. 1) and formulated a metabolic
map of tryptophan metabolism via 5-HT pathway.

MATERIALS AND METHODS

The experimental materials were the synovial fluid, blood and urine of patients who
were diagnosed as rheumatoid arthritis (RA) according to the diagnostic criteria of the
American Rheumatism Association and as osteoarthritis (OA) of the knee joint from clinical
findings, x-ray findings and laboratory data in the Department of Orthopedic Surgery of
Iwate Medical University Hospital.

The experimental methods were as follows:

A. Extraction and measurement of 5-HT were carried out by the method of Davis
et al. (1964) using a weakly acidic cation exchange resin and the method of Udenfriend
et al. (1958) using ZnSO₄-NaOH, respectively.

B. Monoamine oxidase (MAO) activity in the synovial fluid was measured by the
method of Udenfriend et al. (1958).

C. 5-HIAA in the synovial fluid, blood and urine was measured by the method of
Udenfriend et al. (1958).

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RESULTS

5-HT levels in blood and synovial fluid (Table 1)

5-HT level in the synovial fluid as measured by the method of Davis et al. was 0.53±0.26 (mean±s.d.) µg/ml in 8 patients with RA and 0.49±0.13 µg/ml in 13 patients with OA, and that by the method of Udenfriend et al. was 0.58±0.19 µg/ml in 12 patients with RA and 0.42±0.22 µg/ml in 14 patients with OA. These results showed no significant differences between RA and OA.

On the other hand, 5-HT level in whole blood by the method of Udenfriend et al. was 0.57±0.14 µg/ml in 9 patients with RA, 0.54±0.11 µg/ml in 10 patients with OA, and 0.54±0.07 µg/ml in 5 controls.

<table>
<thead>
<tr>
<th>Method used</th>
<th>Number of cases</th>
<th>Blood (µg/ml)</th>
<th>Synovial fluid (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>9</td>
<td>0.57±0.14</td>
<td>0.58±0.19</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>10</td>
<td>0.54±0.11</td>
<td>0.42±0.22</td>
</tr>
<tr>
<td>Control</td>
<td>5</td>
<td>0.54±0.07</td>
<td></td>
</tr>
</tbody>
</table>

Recovery: 82.4% (Davis's), 79.5% (Udenfriend's), 84.5% (Udenfriend et al's)
MAO activity in the synovial fluid (Table 2)

MAO activity in the synovial fluid was 29.00±13.27 μg/ml/hr in ten patients with RA and 74.19±19.61 μg/ml/hr in ten patients with OA. That is, MAO activity in synovial fluid of the patients with OA was about twice as high as that with RA.

**Table 2. Monoamine oxidase activity in the synovial fluid in joint diseases (mean±S.D)**

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Synovial fluid (μg/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>10</td>
<td>29.00±13.27</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>10</td>
<td>74.19±19.61</td>
</tr>
</tbody>
</table>

5-HIAA levels in blood, synovial fluid and urine (Table 3)

5-HIAA level in plasma was 0.38±0.15 μg/ml in 8 patients with RA, 0.32±0.15 μg/ml in 9 patients with OA, and 0.33±0.11 μg/ml in 7 controls. On the other hand, 5-HIAA level in the synovial fluid was 0.23±0.05 μg/ml in 12 patients with RA, and 0.25±0.06 μg/ml in 11 patients with OA. These results showed no significant differences among RA, OA and controls.

**Table 3. 5-Hydroxyindole acetic acid levels in the plasma and synovial fluid in cases with rheumatoid arthritis and in cases with osteoarthritis (mean±S.D)**

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Plasma (μg/ml)</th>
<th>Number of cases</th>
<th>Synovial fluid (μg/ml)</th>
<th>Number of cases</th>
<th>Urine (mg/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>8</td>
<td>0.38±0.15</td>
<td>12</td>
<td>0.23±0.05</td>
<td>6</td>
<td>3.05±1.37</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>9</td>
<td>0.32±0.15</td>
<td>11</td>
<td>0.25±0.06</td>
<td>11</td>
<td>5.90±1.88</td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td>0.33±0.11</td>
<td></td>
<td></td>
<td>7</td>
<td>6.37±1.73</td>
</tr>
</tbody>
</table>

Recovery 85.6% 86.5% 84.8%

Fig. 2. Comparison of the metabolic pathways of tryptophan in the synovial fluid in cases with rheumatoid arthritis and in cases with osteoarthritis.
The amount of 5-HIAA in urine for 24 hr was $3.05 \pm 1.37$ mg in 6 patients with RA and $5.90 \pm 1.88$ mg in 11 patients with OA, and this result shows the significant difference between RA and OA ($p<0.01$).

DISCUSSION

Although rheumatoid arthritis is a systemic disease, the symptoms appear mainly in the joint. Therefore, the analysis of chemical constituents in pathological synovial fluid is important to elucidate the pathogenesis. Thus far, 5-HT metabolism has been examined in patients with rheumatoid arthritis and osteoarthritis (Herrmann 1958; Kerby and Taylor 1959).

At present, the pathway proposed by Udenfriend et al. (1958) is generally accepted as the metabolic pathway of 5-HT in the living body. According to his view, 5-HT is derived from tryptophan which is oxidized first to 5-hydroxytryptophan, followed by production of 5-HT by the action of decarboxylase; 5-HT is then oxidatively deaminated by monoamine oxidase (MAO) to produce biologically inactive 5-HIAA, which is excreted into urine as a final metabolite.

Although Tsuchizawa et al. (1969) reported higher values of tryptophan in the synovial fluid of the patient with rheumatoid arthritis than in the patient with osteoarthritis, no significant differences in 5-HT levels were observed between them. This fact seems to indicate that activities of the enzymes such as hydroxylase and decarboxylase in the pathway from tryptophan to 5-HT are higher in osteoarthritis than in rheumatoid arthritis. Since the turn-over rate of 5-HT was found to be higher in osteoarthritis than in rheumatoid arthritis, retarded metabolism of 5-HT in rheumatoid arthritis may contribute to the appearance of symptoms such as pains in the joints.

Although the present study revealed no significant difference of 5-HT level in the synovial fluid between rheumatoid arthritis and osteoarthritis, it is presumed that the metabolic change from 5-hydroxyindole acetaldehyde to 5-HIAA proceeds faster in rheumatoid arthritis in view of the fact that the activity of MAO for 5-HT was higher in osteoarthritis.

The total amount of 5-HIAA excreted in 24-hr urine and its level per ml (Haverback 1956) were lower in rheumatoid arthritis than in osteoarthritis and in controls. This seems to be due not only to the difference in MAO activity, which is related to the breakdown of 5-HT, between rheumatoid arthritis and osteoarthritis, but also to the effects of hepato-adrenocortical functions (Spiera 1966; Toba 1970).

References


