

## A RADIOAUTOGRAPHIC STUDY OF POSTNATAL DEVELOPMENT OF THE TONGUE FOLLOWING 5-FLUOROURACIL ADMINISTRATION IN MICE.

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### I. INTRODUCTION

Since the synthesis of 5-fluorouracil, a pyrimidine analogue, by Puschinsky et al. in 1957, 5-Fluorouracil, an antimetabolic agent, has been studied by many investigators as an antitumor agent for its clinical side effects as well as teratogenic activity.

Antitumor activity and its side effects of 5-FUR have been prepared and studied by many investigators<sup>5, 6, 7, 9, 14, 16-25, 29, 31, 43, 46, 49, 50, 52, 54</sup>.

On the other hand, teratogenic activity of 5-FUR was reported by many investigators<sup>10, 11, 12, 13, 28, 30, 32, 51</sup>. They reported that 5-FUR produced leg and tail deformities, polydactyly, macrodactyly, oligodactyly, syndactyly, hypodactyly, and micrognathia, and cleft palate.

Stenram<sup>56</sup> studied fine structure in liver cells of rat injected with 5-FUR together with RNA and protein synthesis.

Kugler et al.<sup>31</sup> observed an enlargement of pancreas in 5-FUR treated animals.

Martin et al.<sup>45</sup> studied a light and electron microscopic study of the structural effects of 5-FUR administered pancreatic acinar cells.

Kim and Han<sup>36, 37, 38</sup> studied the effects of the synthetic polynucleotides in exocrine glands of rodent treated with 5-FUR and especially observed a sharp decrease in amylase content of the rat parotid gland.

Kim<sup>35</sup> studied incorporation of Uridine-H<sup>3</sup> and Leucine-C<sup>14</sup> by digestive gland cells of mice treated with 5-FUR by using a modified double emulsion and double

isotope radioautographic technique. Anand<sup>11</sup> studied an electron microscopic and histochemical study of rat Brunner's glands following 5-FUR administration.

Levin<sup>42</sup> observed a decrease in mitotic activity of the rat's small intestine following 5-FUR treatment.

Cho and Han<sup>8</sup> studied, in the light of broad side effects of 5-FUR on rapidly developing cells, the postnatal development of cranial base following fluorouracil administration in mice.

In human, 5-FUR is one of the pyrimidine analogues which has found its use in cancer chemotherapy only except their considerable toxic manifestation.

In animal organ, 5-FUR is taken up in greatest concentration by tissues where there is rapid cell multiplication, i.e. developing, growing and regenerating tissues. In low doses it inhibits formation of new cells and nucleic acid biosynthesis.

The experiment reported in this paper was undertaken with the objective to investigate the possibility of inhibition on the early postnatal development of mouse tongue papillae following 5-FUR administration by using histologic and autoradiographic analysis of thymidine- $H^3$  incorporation.

## II. METHODS AND PROCEDURES

Twenty postnatal mice of Balb/C strain were used in this experiment and were divided into 2 groups of 10 each: the experimental group was given two daily intraperitoneal injections of 25mg/kg body weight of 5-FUR, while the control mice were given similar injections of vehicle alone.

Two hours prior to sacrifice each mouse received an intraperitoneal injection of  $H^3$ -TDR in the amount of  $5\mu$  Ci per gram body weight. The specific activity of this preparation was over 9.0 Ci/mM. Two pairs of the experimental and control mice were sacrificed on days 1, 3, 7, 14, and 21 following the last injection of 5-FUR or vehicle. Mice were killed by decapitation and their head fixed in 4% formalin. Following fixation, the tissues were decalcified in 0.5M EDTA, and double embedded in parlodion and paraplast.

Following the parasagittal serial sections were made at  $10\mu$ , slides were prepared for histologic and autoradiographic observations.

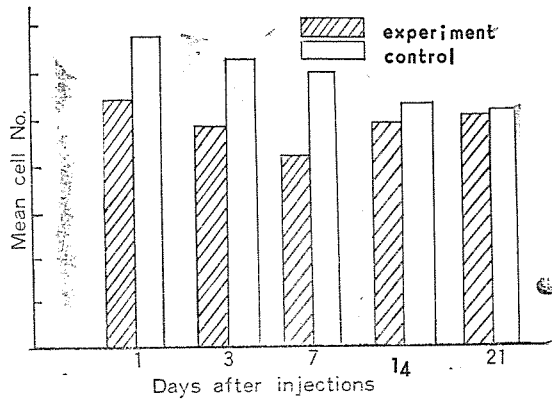
For histological study, slides were stained with hematoxylin and eosin, or Masson's trichrome, while the slides for autoradiography were coated with Kodak NTB-3 nuclear track emulsion and processed in a routine manner (Han's, 67). After three weeks of exposure in refrigerator, the slides were developed and studied by comparing the percentage of labeled nuclei between the experiment and control in the tongue basal layers.

## III. RESULTS

In order to study the developing characteristics of the tongue, quantitatively we

FREQUENCY OF LABELED CELLS IN AUTORADIOGRAPHS OF  
THE TONGUE BASAL LAYER.

Day	Experiment		Control		% of Control
	mean cell No.	S.D.	mean cell No.	S.D.	
1	54.4	8.5	67.2	10.4	80.9
3	48.0	7.2	62.4	9.7	76.9
7	40.8	6.4	61.6	9.2	66.2
14	48.0	7.2	52.0	8.1	92.3
21	48.3	7.5	48.8	7.6	98.9



obtained the following results from the radioautographic observations

Labeled cells appeared more in filiform papillae, fungiform papillae than in vallate papillae in number.

The control groups show that there is an decrease in labeling index throughout experimental days. In the experimental group which was treated with 5-fluorouracil (25mg/kg), the labeling index shows decrease until 7 days, and then increase gradually. On day 1st after 5-FUR injection, experimental group showed 80.9% of control. On day 3rd, it showed 76.9% respectively.

On the 1st week after injection, it showed 66.2% of control and then, it reached the lowest of all in this experiment.

Gradually increasing, it showed 92.3% on day 14.

On the 3rd week after injection it showed 98.9% and experimental group became almost equal to control.

Microscopic observations;

Day 1: There were no significant differences between the control group and the experimental one.

Day 3: In the control group there was beginning of keratinization on the superficial layer of the tongue, and cells in taste bud was shown round and oval in the experimental one. There was retardation of keratinization of superficial layer of the tongue, and cells in taste bud was shown oval, and the demarcation with adjacent cells was unclear.

Day 7: In several areas, newly formed gustatory cells were found in control group but none in the experimental one.

In the experimental group, there was retardation of downward growing foliated gutter of the tongue epithelium.

Vertical and longitudinal muscle fibers showed blunt atrophy while they were well developed in control group.

Day 14: In the control group, there was an increase of fungiform papillae in number than in the experiment.

There was good developmental taste bud, especially increasing in number of gustatory cells in control group.

In the experimental one, gustatory cells were somewhat scarce in number.

Day 21: No significant differences were found.

#### IV. DISCUSSION

5-FUR is the nucleotide analogue which inhibits nucleic acid and protein synthesis as tumor inhibiting compound.

The radioautographic study was used in order to see the differences in the ability to synthesize nucleic acid of the tongue papillae in 5-FUR treated mice.

From the labeling indexes of experimental mice in this experiment index showed 40.8 and showed 66.2% in comparison with control on the 1st week after injection. The lowest labeling index shows that the nucleic acid synthesis of the cells in the tongue epithelium decreases mostly in the experiment on the end of the 1st week. And then the increase of labeling index on days 14 and 21 suggests that the nucleic acid synthesis of the cells was recovering during the experimental period until few difference was seen on day 21.

Although many studies have been made on the clinical effects of 5-FUR<sup>5, 6, 7, 9, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 29, 31, 43, 46, 49, 50, 52, 54</sup> and its toxic effects<sup>10, 11, 12, 13, 28, 30, 32, 51</sup> extensively registered in the tissues having rapid turnover: viz, the bone marrow, skin and gastrointestinal mucosa, they were mostly experiments on adult systems and there were few studies<sup>8</sup> dealt with the effects of 5-FUR on young developing tissue.

Since malignant growth occurs in young individuals as well as pregnant mothers, effects of 5-FUR on craniofacial growth of fetal or early postnatal subjects are important in developing rational approaches to chemotherapeutic regimen.

Martin<sup>44</sup> reported that there was about four times the number of labeled cells in the epithelium of the dorsum as in the undersurface, indicating a greater degree of replacement of surface squamous cells in response to the greater mechanical wear on the dorsum of guinea-pig tongue.

State et al.<sup>55</sup> showed that where the foliate papillae were destined to develop in the tongue of the albino rat the epithelium began to grow deeply into the underlying mesenchymal tissue in the form of solid epithelial ingrowths and followed on the 2nd day of postnatal life by the early appearance of taste buds in the form of cellular collections within the solid downgrowth.

Five types of cells were described in the developing buds.

In renewal of cell populations in the thymidine-H<sup>3</sup> injected female mouse, Walter<sup>59</sup> reported that most cells in the basal layer of tongue epithelium were

radioactive in one day after injection.

At the sides of the tongue, where the stratified squamous epithelium had a relatively flat surface, radioactive cells had moved out from the basal layer at three days and were about halfway to the surface in the 4th day.

By the 8th day the line of radioactive cells had reached the squamous layer and could not be traced further due to the lack of nuclei in the squamous layer.

Quastler and Sherman<sup>53)</sup> reported that the average life span of taste cell is longer than that found for mouse intestinal epithelial cells.

Delorenzo<sup>15)</sup> concluded that his experiments did suggest a rather rapid turnover in the foliate papillae and his preliminary data suggested that the number of labeled cells within the taste bud of the rabbit foliate papillae is greatest between 100 and 200 hours after triated thymidine injection.

Bertalanffy<sup>4)</sup> stated that the turnover time for the total cell population of the superior tongue surface of the mouse was between 4 and 8, 4 days.

An intense alkaline phosphatase reaction is present in the superficial epithelium of the newborn rat in which taste buds are absent.<sup>63)</sup> Taste buds do not appear in the vallate papillae of the rat until the 8-10 postnatal day although a subepithelial nerve plexus is present prenatally.<sup>61)</sup>

No alkaline phosphatase activity was demonstrated in the superficial epithelium associated with the taste buds in the fungiform papillae on the anterior portions of the tongue<sup>62)</sup>.

## V. CONCLUSION AND SUMMARY

The present study is to evaluate, by means of quantitative radioautography utilizing thymidine-H<sup>3</sup>, the effects of 5-fluorouracil on protein and nucleic acid synthesis in postnatal mouse tongue.

Twenty postnatal mice of Balb/C strain were used and were divided into 2 groups of 10 each; the experimental group was given 2 daily injections of 5-FUR (25mg/kg of body weight.)

As a tracer, injection of thymidine-H<sup>3</sup> was used in the amount of 5 $\mu$  Ci/gram body weight. Pairs of the experimental and control mice were sacrificed on days 1, 3, 7, 14 and 21 following the last injection of 5-fluorouracil or vehicle.

The experimental results permit the following conclusions;

1. The effect of 5-fluorouracil on nucleic acid and protein synthesis of basal cell layer of the mouse postnatal tongue decreased from 1st day after experiment. On the first day 80.9% was shown in comparison with control, 76.9% on day 3, 66.2% on day 7 which was lowest in the experiment. Since then the recovery was beginning: 92.3% on day 14, 98.9% which is almost near to the control on the day 21.
2. The effects of 5-fluorouracil on the tongue papillae showed suppressions in the

following order; vallate papillae, fungiform papillae, and filiform papillae.

3. In this study might be concluded that 5-fluorouracil inhibits nucleic acid and protein synthesis of basal cell layer of the mouse tongue and affects postnatal development of the mouse tongue.

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## 5-Fluorouracil 이 白鼠 舌 發育에 미치는 영향에 관한 自記放射法的 研究

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張 相 憲

新生의 Balb/C strain 白鼠 20頭를 使用하였고, 實驗群과 對照群으로 區分하여 實驗群에는 5-fluorouracil의 體重 25mg/kg 씩 2회를 腹腔內注射하였다. 實驗群과 對照群에 모두 犧牲 2時間前에 體重 30%當 5 $\mu$  Ci의 thymidine-H<sup>3</sup> (specific activity는 9.0 Ci/mM 이상)를 腹腔內 注射하였다.

各群은 5-fluorouracil 最終注射後 1, 3, 7, 14, 21日 間隔으로 犧牲시키고, 頭部를 4% formalin에 固定하였다. 組織을 0.5M EDTA에 脫灰하고 parlodion과 parplast에 二重 埋沒을 하여 Parasagittal serial section을 10 $\mu$ 의 切片을 만든 後 自記放射用標本을 製作하였다.

其 結果는 다음과 같다.

1. 5-fluorouracil 이 白鼠舌의 基底細胞層의 核酸合成 및 蛋白質合成에 미치는 影響은 實驗初日인 第1日 부터 억제하기 始作하여 (80.9%) 第3日이 76.9%이고, 第7日이 가장 極甚하고 (66.2%) 其後부터는 多少回復되기 始作하여 第14日이 92.3%이고, 第21日이 98.9% 로서 거의 對照群數値에 接近하였다.
2. 5-fluorouracil은 舌乳頭中 vallate papillae 成長에 가장 억제적 現象을 보였고, 그 다음이 fungiform papillae, filiform papillae의 順位였다.
3. 5-fluorouracil 이 白鼠舌의 基底細胞層의 核酸合成을 억제함을 알 수 있고, 아울러 白鼠舌의 早期 成長 發育에 影響을 줌을 알 수 있다.

### —EXPLANATION OF FIGURES—

- Fig. 1. The radioautograph of the postnatal tongue epithelium on day 1 in the control group. (x 400)
- Fig. 2. The radioautographic postnatal mouse tongue epithelium on day 1 in the experimental one. (x 400)
- Fig. 3. The radioautograph of the control foliated gutter on day 3. (x 400)
- Fig. 4. The radioautographic foliated gutter on day 3 in the experimental group. (x 400)
- Fig. 5. The labeled cells of the postnatal mouse tongue basal layer on day 7 in the control group. (x 450)
- Fig. 6. The labeled cells of the experimental tongue basal layer on day 7. (x 450)

장상헌 논문 사진부도

