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HISTOLOGICAL SURVEY OF THE HEALING PROCESS ON TOOTH EXTRACTION WOUNDS IN RATS AFTER HYPOTHALAMIC MEDIAN EMINENCE LESION.

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ABSTRACT: The purpose of this study was to verify the healing process of tooth extraction wounds in rats which had been injured on the hypothalamic median eminence, compared to a control group. It was found that in a short time (3 to 6 days) the lesion did not provoke changes in sockets healing. The most significant result happened during the period of 18 and 21 days with a delay in the sockets healing.

KEY-WORDS: Sockets healing; median eminence; pituitary gland.

Since the discovery of the hypophysial portal system by POPA & FIELDING (1930; 1933), the participation of this system in the pituitarigenic secretion through releasing factors or neurosecretion (MARSHALL, 1942; SHARRER & SHARRER, 1954; OLIVECRONA, 1957) and the necessary feedback for the endocrine regulation (GUILLEMIN, 1959; GUILLEMIN *et alii*, 1962) many researchers have been concerned with analysing the system involvement inherent to this mechanism.

The hypothalamic median eminence is an area with many nervous endings in which the releasing agents area are secreted and caught by the hypophysial portal system and help in the command of the adenohypophysis of its tropic hormones. There is some doubt about the time that this pituitarigenic function takes independent from the median eminence (SHINDLER, 1962; McCANN & PORTER, 1969). The irregular functioning of the internal secretion glands affects deeply the post-birth ossification chronology and the epiphysial fusion (MELLMAN *et alii*, 1959). SUBIRANA PITA (1975) observed that the lack of pituitarigenic hormones which are mostly concerned with metabolism caused jaws atrophy and reduction on the volume of the gum.

The osseous neoformation of sockets after dental extraction has been analysed in many experimental and/or clinic conditions (MEYER, 1935; CHRISTOPHER, 1942; AMLER *et alii*, 1960; PIETROKOVSKY, 1967; BARROSO *et alii*, 1972; OKAMOTO & RUSSO, 1973). According to the authors this neoformation has distinct phases, following the sequence: 1. coagulum formation and proliferation of the cells from the connective tissue; 2. formation of the healing connective tissue; 3. ossification phase.

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Considering that there is no work related to hormonal reduction with alveolar osseous neoformation after dental extraction, we intend to study, histologicaly, the healing process in rats after hypothalamic median eminence lesion.

MATERIAL AND METHOD

Fourty-eight young male rats (*Rattus norvegicus, albinus*, Wistar), weighing 160-210g were used. The animals were maintained in adequate conditions in individual cages with plenty of water and fed with minced ration (BATAVO) added to minced peanut and sunflower seeds in the following proportion: 60% ration, 20% peanuts and 20% sunflower seeds. The animals were divided equitably in 2 groups: I. Control group; II. Experimental group (hypothalamic median eminence lesion). Feeding was interrupted 24 hours before all surgical proceedings and during this period one dose of 80.000 U.I. Pentabiotic (Fontoura Wyeth) was administered via intramuscular.

In group II, animals were anesthetized with Sodium Pentobarbital at 3% in a 45 mg/kg dose of body weight, I.P. After that they were fixed in the stereotaxic instrument (DAVID KOPF INSTRUMENTS, Calif., USA). The hypothalamic lesion was made in the tuber cinereum median eminence to which the localization of the plans established by De GROOT (1959) was used, and according to the technique described by McCANN & FRUIT (1957). A current of 6 mA was used in the lesion during 20 seconds at each side of the median line, having as central reference, the bregma area. The elethrothermic current was administered to a steel unipolar eletrode 0.5 mm diameter, introduced inside the brain at a 7° angle from a vertical line and going straight to the median eminence.

After the lesion, animals were placed individually in metabolic cages for 24 hours, what made it possible to collect the urine produced during this period. Graduated drinking places enabled us to verify the water consumption. The animals from group I went through the same steps that the ones from group II did, but the use of the current lesion.

After the period of 48 hours, the animals were anesthetized with sulfur ether and the superior right incisors were extracted with the use of appliance proclaimed by OKAMOTO & RUSSO (1973). The wound edges were sutured with silk thread. Four rats of each group were killed with sulfur ether at the following periods, after extraction: 3, 6, 9, 12, 18 and 21 days.

Processing of the parts for histological study consisted first, of separating the right handside of the jaw at the level of the medial sagittal plan. The parts which were taken with intact dental sockets were fixed into neutral formol at 10% for 24 hours (LILLIE, 1954) and decalcified during 35 days approximately, in sodium citrate solution at 20% and formol at 50% in equal parts.

After decalcification, the dehydrated and clarified parts were put into paraffin, being ordered so that serial out of the sockets could be made longitudinally. The cuts, of 6 micrometers, were coloured by Harris's hematoxylin and eosin for histological analysis. The sockets were divided into three zones for this analysis: cervical, medial and apical. Observations were guided from the vestibular and lingual sockets tops to the botton of the sockets.

RESULTS

The animals from the experimental group were selected based on their water absorption during the 24 hours after lesion. The efficiency of hypothalamic median eminence lesion was established based on the water absorption during this period of approximately 110 ml and simultaneous increase of diuresis.

In the 3rd day, the animals from the control and experimental groups did not show any difference in what sockets healing was concerned. This period was characterized by the sockets fulfilling by coagulum and small proliferation of fibroblasts. The cen-

tral of the cervical zone appears with a fibrin net and, next to the lingual osseous cortical the presence of remainders of periodontal ligament.

In the 6th day, the sockets of rats from the control and experimental groups were almost fulfilled by blood coagulum. The cervical zone shows, in the areas which are nearer to the osseous cortical. Both vestibular and lingual, fibroblastic and capillary proliferation, characterizing though, a granulation tissue which substitutes part of the blood coagulum. In sockets medial and apical zones, the formation of a granulation tissue is observed, which substitutes partially, blood coagulum. Osteoblastic activity with beginnings of osseous formation is very clear at sockets bottom level.

In the 9th day after the extraction, the sockets central area in the cervical zone is totally fulfilled by granulation tissue for animals from both control and experimental groups. The areas next to osseous cortical either vestibular or lingual of the sockets from the control group showed intense osteoblastic proliferation while in the ones from experimental group, this proliferation is not so intense. The medial and apical zones of the control group were almost totally occupied by osseous tissue and the trabeculae which are nearer the cortical were more mature, the periosteal was formed by discriminated cells, medullary spaces were smaller and occupied by conjunctive tissue less cellularized and more discriminated (Fig. 1). The sockets medial and apical zones from the experimental group showed a great quantity of granulation tissue substituting the blood coagulum. The quantity of osseous tissue which was formed was moderate and situated at the sockets bottom level and in scattered areas of the medial zone. This osseous tissue appeared not to be so mature, presenting cavities occupied by osteocytes, very wide and medular spaces intensely celularized (Fig. 2).

In the 12th day, almost all sockets zones of the control group were occupied by trabecular osseous tissue. The osseous trabeculae of the dental sockets zones showed mature aspect in the area next to the osseous cortical, both vestibular and lingual, and less mature while going towards the more central areas in the dental sockets (Fig. 3). Concerning the experimental group, the sockets cervical zone was almost totally occupied by granulation tissue and/or remaining blood coagulum. The osteoblastic proliferation and the formation of trabecular osseous tissue limits itself to the nearest areas to vestibular and lingual sockets osseous cortical (Fig. 4). The medial and apical zone were occupied by trabecular osseous tissue, which was immature in the sockets central areas. Some remaining areas of blood coagulum were observed in the sockets apical zone.

In the 18th day, the cervical, medial and apical zones of dental sockets of rats from the control group were occupied by compact, mature osseous trabeculae with small, medullar spaces which were not so cellularized, and showing discrete osteoblastic activity (Fig. 5). In the experimental group, the cervical zone of the dental sockets showed moderate quantity of granulation tissue in its central area. The nearest areas to the vestibular and lingual osseous cortical showed osteoblastic proliferation and formation of trabecular bone towards the sockets central area. Some areas of granulation tissue and/or remaining blood coagulum were observed in the medial and apical zones, which were occupied by mature osseous tissue in the areas which are near the osseous cortical and immatures in the center of the sockets. (Fig. 6).

In the 21st day after dental extraction, the alveolar zone of rats from the control group were occupyed by mature, compact osseous trabeculae with small medullary spaces, little cellularized and discrete osteoblastic activity (Fig. 7). Concerning the dental sockets of animals from the experimental group, the apical and medial zones showed trabecular osseous tissue more immature in the sockets central areas. Remaining blood coagulum areas and granulation tissue were observed in the medial and apical zones (Fig. 8).

DISCUSSION

Considering data obtained according to the methodology which is employed in the present work, we could observe that this methodology is adequate to this kind of experiment. The evidence that hypothalamic median eminence lesion was efficient was established based upon data related to water consumption (above 110ml/24 hours). The increase of water absorption in this experimental situation was displayed by McCANN & FRUIT (1957) and McCANN & HABERLAND (1959).

The phenomenon which was observed in the sockets healing process after dental extraction obey a biological sequence which is considered complete when the sockets are fulfilled by recently formed osseous tissue, remodeled sockets top and proliferation of gingival mucosa, developing together to complete sockets covering. This process begins from an hemorrhage which fulfills the dental sockets. The coagulum, which appears in decreasing quantity during the periods considered in this work, does not interfere in the chronology of sockets healing, as it is also observed by many authors (RUSSO *et alii*, 1969; SILVA, 1981). The sockets healing analysis showed that blood coagulum is gradually substituted by granulation tissue and, in the sequence, formation of conjuctive tissue, emergency of osteoid tissue in the sockets apical zone and its transformation in mature osseous tissue, what is according to observations made by LOE (1959), AMLER (1969), PIETROKOVSKI (1967), BARROSO (1977) and CARVALHO (1981).

The presence of remainings from periodontal ligament at the 3rd day after extraction must be pointed out as they are important for the begining of fibroblastic proliferation, which goes from the lingual osseous wall towards the center of the sockets, according to what was also observed by many authors (JOHANSEN & GILHUUS-MOE, 1969; OKAMOTO & RUSSO, 1973; VALDRIGHI *et alii*, 1974; CARVALHO, 1980). In the vestibular face this proliferation starts from the conjunctive tissue of the osseous wall and also goes towards the center of the sockets. Our results, concerning the control group, confirm yet some data which show, histologically, that the healing process of tooth extraction wounds in rats happens in 21 ± 1 days after the extraction and that it is characterized by the shutting of sockets ostium by the gingival mucosa, remodeling of sockets osseous tops and well defined at the level of the three sockets zones.

Nevertheless, the analysis of sockets healing of animals from the experimental group showed that although having developed exactly like the control group until the 6th day after extraction, the presence of more immature trabecular osseous tissue during the following phases, mainly in the central sockets area, focus of granulation tissue and remaining coagulum suggested us that sockets healing in animals which injured in the hypothalamic median eminence did not develop in the adequate time. These observations, partly, coincide to the conclusions of BECKS *et alii* (1946) when they made the pituitectomy, and observed changes in the celular structure of the ameloblast layer, remarkable decrease in the pulp vascularization and increase of cement thickness from the 14th day after the surgery. These manifestations, although they are not analysed in the present work, are useful to show that the effects of pituitectomy take some time to allow demonstration. May be this is the reason why TELES (1959) could not find changes in the sockets healing process after the pituitectomy.

Based on the evidence presented by this work, that the hypothalamic median eminence lesion does not affect significantly the pituitary function at short term and that at long term the manifestations of sistemic abnormalities and the chronology of dental sockets healing suffers a delay, we could suggest a gradual decrease of pituitary hormones. In this aspect, we have the statements by GANONG (1977) who relates the growth hormone (GH) to ion calcium metabolism. According to this author, the GH increases urinary discharge of this ion but also increa-

ses its intestinal absorption; this last action may be more intense than kidney action, resulting into a positive balance of calcium. As a consequence, if there is a decrease of this hormone, calcium absorption will be made with difficulty and its effects upon healing tissues will also be decreased, causing failure in the osseous tissue mineralization, as it was observed during the final periods of this work.

The delay which happens in the development of body bones and soft tissues caused by hypopituitarism was also related to the deficiency of GH by McDONALD (1977). On the other hand, SALOMÃO *et alii* (1974) relates the deficiency of estrogens which operate on enzymatic system and, for this reason, contribute for deficient formation of the calcifyed organic matrix. The formation of this matrix depends mainly on two factors: intensity of osteoblastic activity and disposability of proteinic material. According to our results, osteoblastic activity suffers a light stabilization from the 9th day after dental extraction on.

It must be pointed out that the knowledge of half-life of a hormone does not necessarily gives a sure idea of hormonal action time. Some hormones produce their effects immediately and others with latency of hours perhaps before the events which are considered a physiological answer (MOUNTCASTLE, 1978). Another aspect which deserves some attention is the fact that hormones present effect even when they appear in very low concentrations (MORGAN, 1976). These observations support our hypothesis that although the median eminence lesion made in this work have brought functional changes in the pituitary, the action degree of this gland may have been maintained during some time, what explains the sockets healing almost normal in the initial phase which was considered (from the 3rd to the 6th day after extraction). The osseous tissue immaturity, mainly in the sockets central areas and in the final stages which are considered for our experimental group, is not in accordance to the results of the animals from the control group which presented the sockets with mature osseous trabeculae, with decreased medular spaces not much cellularized and discrete osteoblastic activity.

Histological observations of all sockets in all periods showed that infective processes did not exist. Possibly, during the final periods the ossification patterns have already been introduced, what makes the establishment of this process difficult. If there was a significant decrease of thyroxine in the initial periods, infection could be present due to the fact that animals are more susceptible to this event (TEPPERMAN, 1977). Although they did not make dental extractions, MORAES & MATHEUS (1980) observed that in skin wounds of hypothyroid rats, a delay happens in the formation of granulation tissue confirming previous statement by VOITKEVICH & BUKHONOVA (1961). This defection was related to be lack or decrease of thyroxine which affects proteinic metabolism, proving previous statement by WILLIAMS (1974) that this hormone supports mainly proteinic synthesis. These analysis of our groups clearly shows that granulation tissue is present in a greater quantity in the experimental group than in the control group. This fact may be related to the decrease of thyroxine. This observation had already been made by BARROSO (1970) when he related the delay in the development of the sockets healing process to the decrease of thyroid hormones and by ERNOULD (1954) who related to thyroid hormones a specific role in osseous maturation. Nevertheless we can imagine based on literature, that other hormones take part in this process.

The explanation of the groups of endocrine factors which can act in the healing process in dental extraction wounds will only be possible when specific comparisons between hyper and hypofunction of endocrine glands during this process where analysis of hormonal and histochemical concentration, enzimatic activity and others must be included.

SUMMARY AND CONCLUSIONS

A histological study on the healing process of dental extraction wounds was carried out in rats which had been injured in the hypothalamic median eminence, compared to a control group. The dental extraction was made immediately after verifying the lesion efficacy and animals were sacrificed at the 3rd, 6th, 12th, 18th and 21st days after the extraction. Our results showed that until the 6th day there was no change in the sockets healing process. In the meantime, between the 9th and 12th days, a small delay was observed in sockets healing of animals from the injured group. The most significant result happened during the period of 18 and 21 days with a delay in the sockets healing process, mainly in its central area and apical, cervical and medial zones. These results lead us to conclude that although the lesion had affected pituitary function, concerning osseous neoformation, this disfunction appeared only after a mean period of 11 days.

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RESUMO: Foi estudado histologicamente em ratos lesados na eminência média do hipotálamo, o processo de reparo em feridas de extração dental, seguido de um grupo-controle. A extração dental foi realizada imediatamente após a verificação da eficiência da lesão e o sacrifício dos animais efetuado aos 3, 6, 9, 12, 18 e 21 dias pós-extração. Nossos resultados mostraram que até o 6.° dia não houve alteração no processo de reparo alveolar. No período intermediário, do 9.° ao 12.° dia, foi verificado um atraso discreto na reparação alveolar dos animais do grupo lesado. O resultado mais significativo ocorreu nos períodos de 18 e 21 dias, com um atraso no processo de reparo do alvéolo, principalmente em sua área central e nos terços cervical, médio e apical. Essas detecções levam-nos a concluir que, embora a lesão tenha afetado o funcionamento hipofisário, em termos de neoformação óssea, a manifestação dessa disfunção aparece após um período aproximado de 11 dias.

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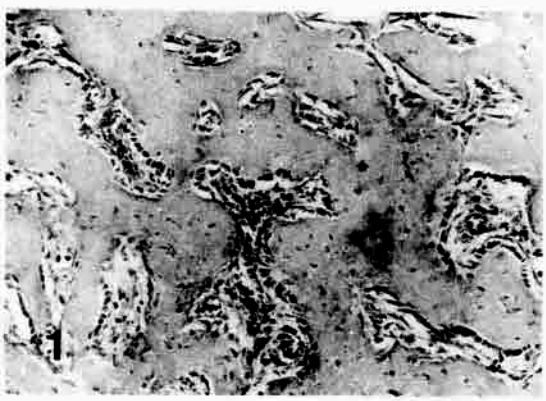


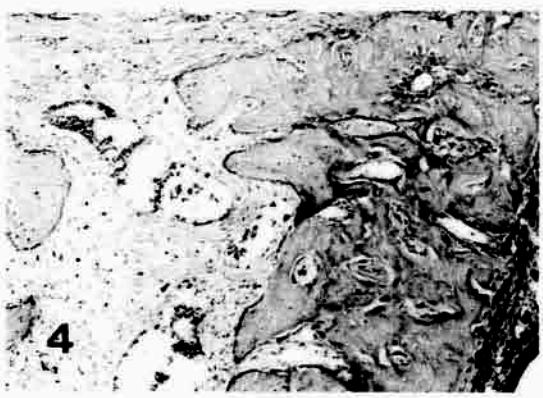
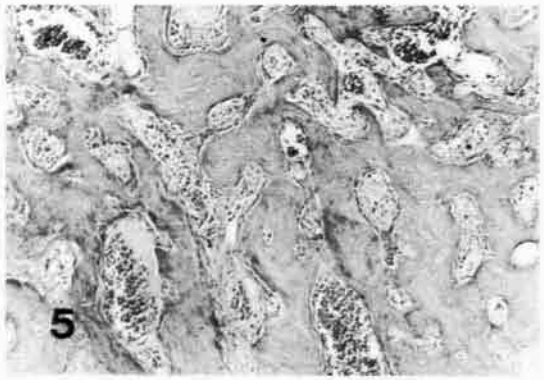


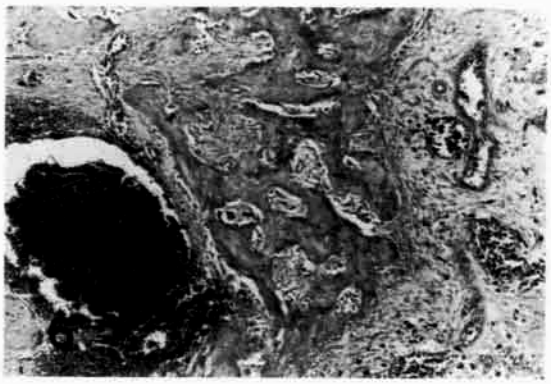
FIG. 1 — Control. 9 days. Medial zone of the sockets. Osseous tissue mature nearer to the cortical osseous vestibular. H.E. ± 100X.

FIG. 2 — Experimental. 9 days. Apical zone of the sockets. Osseous tissue immature. H.E. ± 100X.

FIG. 3 — Control. 12 days. Cervical zone of the sockets. Formation of trabecular osseous tissue of the vestibular osseous cortical to central areas of the sockets. H.E. ± 50X.

FIG. 4 — Experimental. 12 days. Cervical zone of the sockets. Discrete formation of trabecular osseous tissue going of the vestibular osseous cortical to sockets central areas. H.E. ± 50X.





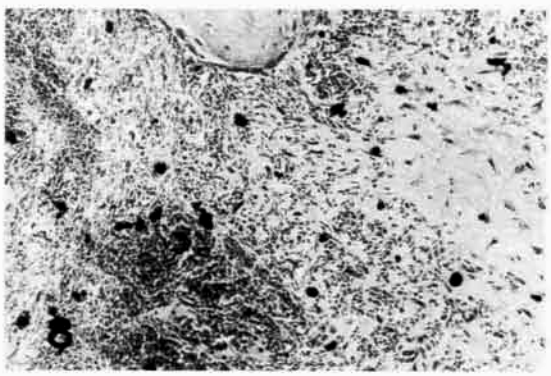


FIG. 5 — Control. 18 days. Cervical zone of the sockets. Osseous tissue mature. H.E. ± 50X.

FIG. 6 — Experimental. 18 days. Medial zone of the sockets. Osseous tissue immature in the central area of the sockets granulation tissue areas and remaining blood coagulum. H.E. ± 50X.

FIG. 7 — Control. 21 days. Cervical zone of the sockets. Osseous tissue mature. H.E. ± 100X.

FIG. 8 — Experimental. 21 days. Medial zone of the sockets. Granulation tissue areas and remaining blood coagulum. H.E. ± 100X.