The Effect Of Thyrotropin Releasing Hormone (TRH) On The Experimental Carbon Dioxide Laser Brain Lesion: Ultrastructural and Biochemical Study

HÜSEYİN BAĞDATOĞLU, FARUK İLDAN, SAİT POLAT, ALP İSKENDER GÖÇER, KÜRŞAT HERGÜNER, KIYMET AKSOY, MEHMET KAYA, SEBAHATTİN HACIYAKUPOĞLU

Çukurova University School of Medicine Department of Neurosurgery (HB, Fİ, KH, AİG), Department of Histology (SP, MK) Department of Biochemistry (KA) Balcalı Adana, Turkey

Abstract : Although the main advantage of the CO_2 laser lies in the possibility of a less traumatic effect on the surrounding tissue, its use in neurosurgery still necessitates a thorough and detailed evaluation of the effect on surrounding normal central nervous system (CNS) tissue. Therefore this study was undertaken to investigate the ultrastructural and biochemical effects of the CO_2 laser on the application area and the surrounding normal central nervous system tissue . Sodium–potassium activated and magnesium–dependent adenosine–5'–triphosphatase (Na+–K+ /Mg 2+ ATPase E.C.3.6.3.1) , magnesium dependent adenosine –5'–triphosphatase (Mg2+ ATPase E.C.3.6.1.3) and calcium activated magnesium dependent adenosine–5'–triphosphatase (Ca2+/Mg2+ ATPase E.C.3.6.1.3) enzymes, superoxide dismutase, light microscopic and ultrastructural findings were determined in dog brain following laser application with and without thyrotropin releasing hormone (TRH) treatment. Laser lesions were created by a CO_2 laser in the cerebrum . Fifteen days later, after thyrotropin releasing hormone injection, ultrastructural and biochemical investigations were undertaken to evaluate the effect of thyrotropin releasing hormone on the laser induced lesion and particularly surrounding cerebral tissue. Ultrastructural findings, showed that thyrotropin releasing hormone reduced degeneration on the CO_2 laser–applied lesion.

Key Words : ATPase, CA2+/Mg2+, CO_2 Laser, dog, Na+-K+/Mg2+ATPase, Mg2+ATPase, superoxide dismutase.

INTRODUCTION

Since laser was introduced as a neurosurgical instrument in 1965 by Rosomoff and Carroll (31), they have been used for many complicated procedures (8,22). Since then the laser has undergone rapid development, resulting in a wide range of different systems. At present , mainly two different types of laser, CO_2 and the neodymium–YAG laser are employed in neurosurgery (4).

The CO_2 laser has been used in neurosurgery by many authors and is established as a useful energy source for cutting and dissection and vaporizing tissue in many surgical procedures (1). CO_2 laser is absorbed well by tissue and is particularly safe and reliable for the removal of solid tumour, providing an excellent cutting effect and causing only slight edematous reaction.

The endogenous opiate system may play a role in the pathogenesis of a number of diseases and affect the pathophysiology of the development of CNS injuries (3,7,13). The opiate receptor antagonist, naloxane has been used to treat cerebral ischemia in limited clinical trials (12) and animal models of stroke (18). Although the mechanism of action was not elucidated , it is tempting to postulate that this is due to a drug–induced improvement in cerebral blood flow, allowing the viable but electrically silent area of the cerebrum to become functional (2). TRH is a partial "physiological" opiate antagonist. It is widely distributed in the CNS (42), that spares analgesic systems (19,20). TRH treatment has been

reported to improve neurological function and EEG disorders following brain–stem compression in the cat (16). It is also reported that TRH significantly improves neurological outcome after traumatic spinal cord injury (14,15). These findings suggest that TRH may play useful part for laser induced lesions in the CNS tissue.

MATERIAL AND METHODS

Thirty adult mongrel dogs of both sexes each weighing 20–25 kg were used in this study. The dogs were divided into four groups and were anesthetized with alpha–chloralose (80 mg per kilogram I.V) .Catheters were placed in the femoral vein for infusion of drugs. First the dogs were placed , in the left lateral position and then in the right lateral position (in groups I and II). Temporal craniectomy on the right and left was performed. The dura mater was carefully incised and reflected, exposing angular gyrus. The same surgical procedure was undertaken unilaterally in the Groups III and IV.

Group I: In five dogs, after bilateral temporal craniectomy , the wounds were closed by layers. Fifteen days later , the dogs were sacrificed.The angular gyrus was removed for histopathological (light and electron microscopy) and biochemical studies.

Group II: Five dogs, following the same procedure as in Group I, were treated with 200 pg/day TRH intravenously (IV) for 15 days. The same tissue as in Group I was removed for histopathological and biochemical studies.

Group III: In ten dogs, following unilateral temporal craniectomy lesions were generated with a commercially available CO_2 laser. (Sharplan 1040, 125 mm focal point handpiece. Laser Ind. Ltd. Tel-Aviv/Israel). The average laser power was l5 W, exposure times were 40 second for the angular gyrus. The diameter of the laser spot was 4 mm . Following laser applications the wound was closed. Fifteen days later, the dogs were sacrificied and the angular gyrus was taken for histopathological examination and biochemical study.

Group IV: Following temporal craniectomy and laser application as in Group III, the dogs were treated with TRH 200 pg/day IV for fifteen days. Then biopsies were taken in the same manner.

Determination of ATPase Activities: After the animals were sacrificed, a sample of brain tissue was removed as rapidly as possible. Ten percent homogenates of the tissue were prepared in 0.3 M sucrose containing 1mM magnesium by homogenising for 90 sec. using a teflon pestle clearance 0.25–0.38 mm at 1000 rpm. ATPase activities were determined on the resulting supernatants by measuring the rate of liberation of inorganic phosphate (Pi) from disodium ATP (29). Incubation media were made up as described previously (30).

Adenosine 5'triphosphatases were as follows: Na+–K+ ATPase (mM)–Mg Cl2 6 , KCL 5 , NaCl 100, EDTA 0,1 , tris–HCL buffer pH 7.4, 135, Ca2+/Mg2+ ATPase, MgCl2 6, CaCl2 0.15, EDTA 0.1, tris HCL buffer pH 7.4, 135.

After preincubation for 5 min. at 37° C disodium ATP was added to each tube to reach a final concentration of 3 mM. The blank samples containing no enzyme, standard and unknowns were incubated at 37° C for 30 min. The reaction was stopped by putting the samples in ice. Inorganic phosphate was determined on 1 ml aliquots of the incubated mixtures by addition of lubrol–malybadate solution followed by vortexing and standing at ambient temperature for 10 min. Extinction at 240 nm was measured . All assays were done in triplicate and run with enzyme and reaction blanks. Samples were compared for phosphate content with standards of KH_2PO_4. Specific activities were calculated as nmol Pi/hr/mg protein.

All reagents were of Analar grade unless otherwise stated. Disodium adenosine 5'–triphosphate (Na_2 ATP) was obtained from Boehringer Ltd. and lubrol type Px was obtained from Sigma Chemical Co. Ltd.

Lubrol–Molybdate solution was prepared according to Reading and Isbir (29,30).

Protein content was determined according to the method described by Lowry (25) and bovine serum albumin was used as a standard.

Measurement of SOD (superixide dismutase) activities:

The preparation of SOD from dog brain was accomplished as described by Weisinger and Fridovich (41). The pyrogallol method was used to measure SOD activity with slight modification as described Roth and Gilbert (32). Specific activities were calculated as U/mg protein.

Electron microscopic study:

Tissues for electron microscopic examinaton were immediately placed in 5 % glutaraldehyde buffered at pH:7.4 with Millonig phosphate buffer (28) for three hours. The tissue pieces were subsequently fixed in 1 % osmic acid for two hours. Tissue samples were then dehydrated in graded ethanols, embedded in araldite and processed for electron microscopy using conventional methods.

Light microscopic study:

The tissue samples for light microscopic study were fixed in 10% formalin solution and then prepared in the routine fashion. Five micron thick slices were taken from paraffin embedded tissue blocks and stained with haematoxylin-eosine.

BIOCHEMICAL RESULTS

SOD levels are shown in Table I. There was no significant difference in the SOD level between Groups I and II ($p>0.05$). We found that in Groups III and IV SOD levels were significantly high compared to Groups I and II ($p<0.01$). In Group IV SOD levels were significantly less than those in Group III ($p<0.01$).

Table: I Superoxide dismutase enzyme activities in the dog brain for each group. (U/mg protein)

I. Group	II Group	III Group	IV Group
817	807	6400	9300
975	760	7000	8950
650	910	5955	7500
590	612	4755	6800
750	575	6200	6200
810	875	7500	7500
915	915	5955	9100
785	702	7020	8200
850	540	7450	8500
740	660	6500	8500
787.8 ± 114.6	735.6 ± 139.0	7930 ± 1042.8	6473.5 ± 826.8*

* The results are expressed as mean ± standard deviation (SD).

ATP ase levels are shown in Tables II to V. There was no significant difference between Groups I and II ($p>0.05$) except for Ca2+/Mg2+ ATPase ($p<0.01$). ATPase levels were significantly low compared to Groups I and II ($p<0.01$). On the other hand in Group IV ATPase levels were significantly higher than those in Group III ($p<0.01$) except for Ca2+/Mg2+ ATPase. Ca2+/Mg2+ ATPase interestingly was low in the TRH treated group compared to Group III .

Table II: Specific activities of Na+–K+/Mg2+ ATPase, Mg2+ ATPase and Ca2+/Mg2+ ATPase in Group I (nmpi/mg/h prot.).

Na+–K+/Mg2+ ATPase	Mg2+ ATPase	Ca2+/Mg2+ ATPase
1333	1500	1800
1540	1700	2040
1750	1810	2100
1660	1975	1790
1296	1990	1810
1430	1415	1805
1330	1510	1740
1540	1450	1690
1710	1396	1700
1896	1600	1750
1548.5 ± 203.3	1624.6 ± 217.3	1822.5 ± 137.7*

* The results are expressed as mean ± standard deviation (SD).

Table III: Specific activities of Na+–K+/Mg2+ ATPase, Mg2+ ATPase and Ca2+/Mg2+ ATPase in Group II (nmpi/mg/h prot.).

Na+–K+/Mg2+ ATPase	Mg2+ ATPase	Ca2+/Mg2+ ATPase
1240	1460	1600
1380	1500	1986
1290	1810	1680
1502	1392	1340
1720	1350	1530
1568	1902	1650
1312	1775	1750
1896	1510	1240
1696	1490	1320
1398	1440	1440
1500.2 ± 216.0	1562.9 ± 192.2	1553.6 ± 227.2*

* The results are expressed as mean ± standard deviation (SD).

Table IV: Specific activities of Na+–K+/Mg2+ ATPase, Mg2+ ATPase and Ca2+/Mg2+ ATPase in Group III (nmpi/mg/h prot.).

Na+–K+/Mg2+ ATPase	Mg2+ ATPase	Ca2+/Mg2+ ATPase
526	376	833
444	450	784
496	375	800
510	440	775
400	398	840
396	475	910
375	450	896
560	402	795
475	502	855
400	490	880
458.7 ± 64.2	437.3 ± 47.7	836.8 ± 48*

*The results are expressed as mean ± standard deviation (SD).

Table V: Specific activities of Na+–K+/Mg2+ ATPase, Mg2+ ATPase and Ca2+/Mg2+ ATPase in Group IV (nmpi/mg/h prot.).

Na+–K+/Mg2+ ATPase	Mg2+ ATPase	Ca2+/Mg2+ ATPase
606	614	757
598	676	780
617	644	796
708	714	728
716	576	696
604	675	686
526	697	797
492	596	702
608	618	796
598.7 ± 74.8	645.4 ± 44.9	753.6 ± 46.3

* The results are expressed as mean ± standard deviation (SD).

ULTRASTRUCTURAL FINDINGS

Group I: Normal cellular ultrastructure have been observed in the cells of brain tissue (Fig.1).

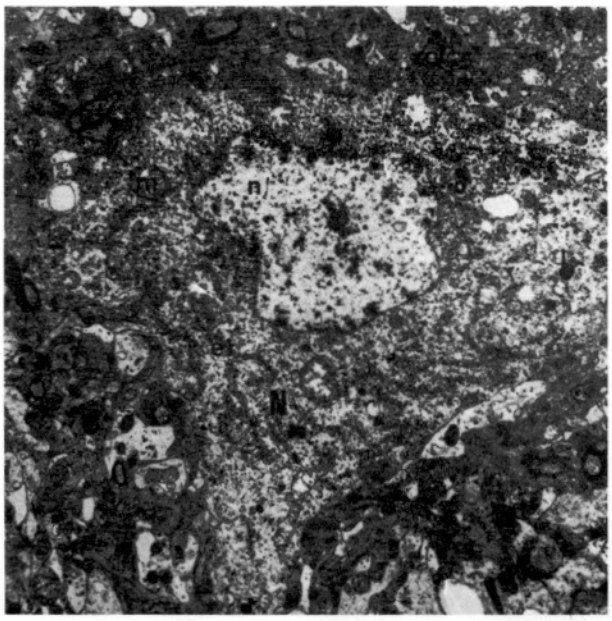

Fig. 1 : Group I. Normal dog brain. The nerve cell (N) shows a vesicular nucleus (n) and prominent cytoplasmic organelles including mithochondria (m), granular endoplasmic reticulum (er) and lysosomes (l). Axon (a) X 4500

Group II: Structure of the brain tissue was similar to that in Group I.

Group III: Although most of the nerve cells exhibited normal ultrastructure including nuclear and cytoplasmic organelles, the myelinated nerve fibers were significantly degenerated. The myelin sheaths lamellae were separated from each other and there were variously sized spaces between them . Some of the nerve fibers showed focal myelin sheath degeneration. Also, they exhibited minimal axonal structural changes. Glial cells showed normal structure according to their nuclei and cytoplasmic organelles (Fig.2). Although capillary endothelial cells and the capillary basal lamina exhibited normal structure, the pericyte cytoplasm revealed excess of lysosomes and lipofuchsine granules . Also large interstitial spaces were seen around the cells and the capillary vessels indicating edematous areas (Fig.3).

Group IV: In general, the nuclei and cytoplasmic organelles of the nerve cells showed normal structure. Although small–sized nerve fibers revealed normal structure, large sized ones showed moderate myelin sheath degeneration. There were interstitial spaces around the nerve and glial cells where nerve fibers degeneration was prominent. The wall of the capillary vessel exhibited normal structure. Variously

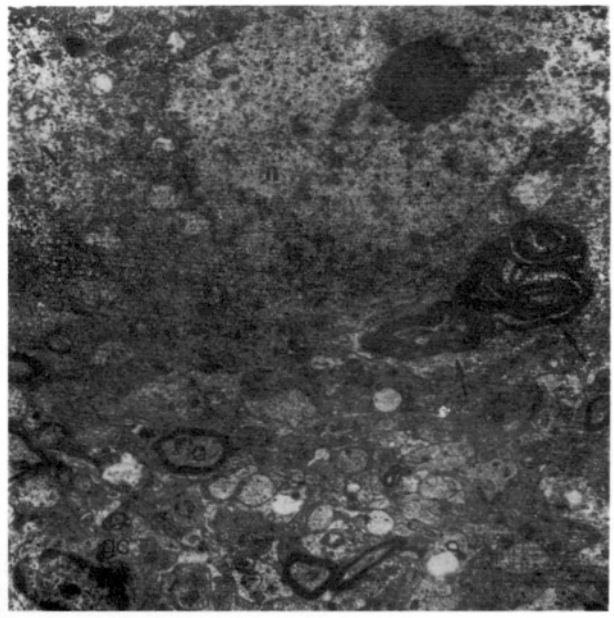

Fig. 2 : Group III. CO_2 laser aplicated dog brain. The nucleus (n) and cytoplasmic organelles of the nerve cells (N) are seen normal structure. The large myelinated nerve fibers show separation of the myelin lamellae (arrows). Axon (a), glia cell (Gc) X 6600

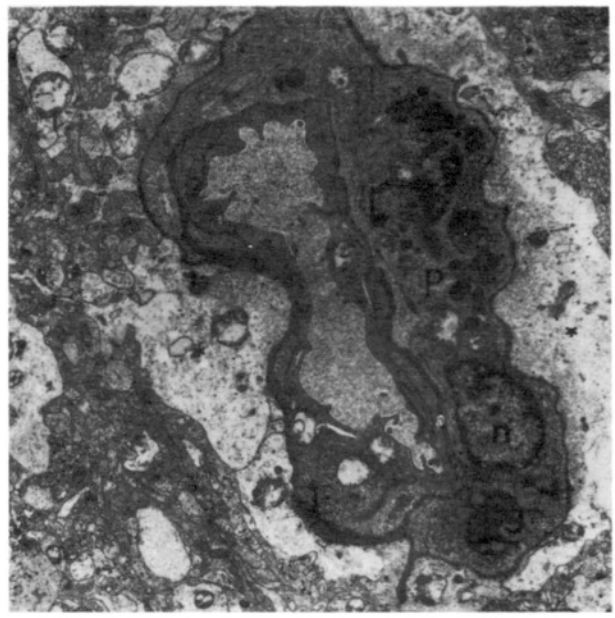

Fig. 3 : Group III. CO_2 laser applicated dog brain. The pericyte (P) cytoplasm shows an excess of lysosomes (l) and lipofuchsine granules (Lg). Large interstitiel spaces are seen around the capillary. Nucleus (n), Endothel (E). X 6600.

sized spaces were also seen around the capillary vessel indicating edematous areas (Fig.4).

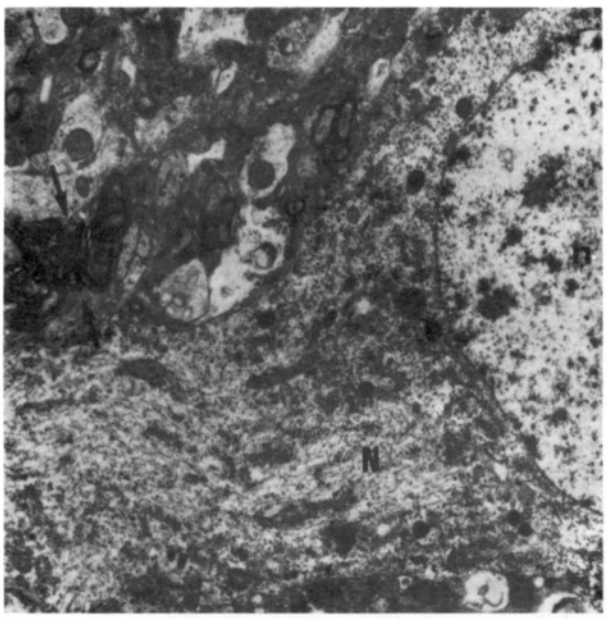

Fig. 4 : Group IV. CO_2 laser and TRH applied dog brain with the treatment. The nucleus (n) and cytoplasmic organelles of the nerve cell (N) are normal. Large sized nerve fibers show moderate myelin sheath degeneration (arrows) Axon (a) X 6600.

Light microscopic findings:

Group I: The control group showed normal brain tissue findings.

Group II: The findings were the same as Group I.

Group III: Polymorphonuclear leucocyte infiltration and proliferation in the capillary vessels were found, indicating inflammatory granulation in this roup.

Group IV: Inflammatory granulation, congestion in the vessels and edema were observed.

DISCUSSION

The introduction of various surgical laser systems is an exciting advance in neurosurgical instrumentation and technique. The use of lasers is based on the conversion of light energy into heat in tissue. The degree and extent of the thermal action is determined by the optical and thermal properties of the tissue, the geometry of the laser beam and the energy of the incident light. Thermal interaction is of primary importance for surgical applications. The structure and function of living cells depend on the presence of a wide variety of proteins. These molecules which are energetically stable at body temperature enter a higher energy state if the local temperature is raised to near 50°C or more. Following irreversible thermal denaturation protein molecules lose their ability to function within the cell.

A CO_2 laser has a wavelength of 10.6 microns which is well established as a useful energy source for coagulating and vaporizing tissue. CO_2 laser has been considered the best for neurosurgery among surgical lasers because it efficiently vaporizes tissue. CO_2 laser is entirely absorbed due to the specific wavelength at the surface and completely converted into heat. It is therefore highly suitable for tissue ablation and focuses to form a cutting instrument with little reaction on surrounding tissue.

In our study, brain tissues in the Groups I and II were normal in macroscopical appearance. The angular cortex of the dogs was hit by the focused laser beam in Group III and IV and a crater was made of 5X5X5 mm. Fifteen days later, this crater in the angular gyrus was filled by proliferation of glial tissue. There was no difference in appearance between Groups III and IV. Boggan (5) reported that the blood–brain barrier which is disturbed by laser returned to normal in 24 hours, and laser applied area was filled by proliferation of the glial tissue as in our study. Tiznada et al. (35) reported that following CO_2 laser application with a power output of 40 W, duration 4 sec, increased interstitial areas , haemorrhagic necrosis in the parenchyma, disturbance of the blood–brain barrier, arterial and venous occlusion, increased local pressure and stasis were found. All these findings peaked for 24 hours, then decreased gradually (36). Ultrastructural findings in our series are similar to those previously described by Tiznada et al. (35,36). But in Group III, structural changes within cells of the brain and arterial tissue and intersititial spaces indicating edematous area were found more than to those in the Group IV. In Group IV, ultrastructural findings of the brain tissue showed that there was only very little degeneration possibly due to the effect of the TRH. TRH , a partial physiological opiate antagonist is widely distributed in the CNS (21,35). We postulated that the beneficial effect of TRH in laser lesions may be by direct neuronal action (membrane stabilization by opioid receptor or nonopioid receptor antagonism) or indirectly by increasing CBF above the critical ischaemic threshold. On the other

hand TRH is also a glutamate antagonist which may explain the suggested beneficial effect.Our findings suggest that TRH may be useful for limiting the extent of tissue injury.

Following ischaemic or traumatic brain damage, polyunsaturated fatty acids increase in the intracellular and extracellular space parallel to the severity of the trauma (17,23,24,26). Oxygen–free radicals are implicated as mediators of ischaemia–reperfusion injury of various tissues including spinal cord and brain tissue (9,10,27). It is reported that initially, phospholipase is activated followed by release of free arachidonate (40). An increase in phospholipase C activity was determined in cat brain after experimental brain injury (40). Then the metabolism of arachidonate via cyclo–oxygenase is accelerated evidenced by an increase in prostaglandin concentration shortly after injury (11). The cerebral arteriolar abnormalities mainly included sustained dilatation, reduced vasoconstrictor responses to arterial hypocapnia, decrease or loss of vasodilatator responses to arterial hypotension, focal morphological lesions in the endothelium and vascular smooth muscle and reduced vessel wall oxygen consumption and breakdown of the blood–brain barrier to plasma proteins and other macro molecules (37,38). Superoxide and its products in this brain injury originate from accelerated arachidonic metabolism via cyclooxygenase (39). Superoxide dismutase is a specific scavenger of superoxide and removes the radical by catalyzing its dismutation to form hydrogen peroxide and molecular oxygen, in turn ,catalase starts conversion of the hydrogen peroxide to molecular oxygen and water. Therefore we undertook this study to evaluate directly the production of superoxide dismutase after brain injury by laser and to examine its changes according to the treatment of TRH in the injury. We postulated that SOD levels were related to regeneration of brain tissue and TRH treatment improved SOD levels. Schettini et al. (33) reported that SOD levels peaked (fivefold) at 60 minutes after the lesion, slowly decreased (twofold) at 150 minutes, then rebounded gradually (threefold) at 24 hours. We determined the SOD levels in all Groups at the fifteenth day. The high level (tenfold) in Groups III and IV even on the fifteenth day may be due to late rebound.

ATP ase systems play an important role in the ionic and osmotic balance and active transportation of the cell. Recent studies have demonstrated that one consequence of trauma to the CNS is increased lipid peroxidation and decreased activity of the critical membrane–bound enzymes (6,34). Phospholipids in cell membrane are known to be responsible for activities of some membrane bound enzymes, therefore their activities decrease in the damaged tissue. We postulated that ATPase systems were affected by CO_2 laser and TRH treatment improved this systems.

CO_2 laser application in normal brain tissue causes degeneration and TRH partially corrects this degeneration as evidenced by ultrastructure findings and SOD and ATPase levels. Our conclusion is that TRH might be of beneficial value in limiting laser lesions of CNS tissue.

This study was presented at the 7. Turkish Neurosurgery Congress .

Correspondence: Hüseyin Bağdatoğlu, M.D.
Çukurova University School of Medicine
Department of Neurosurgery
Balcalı Adana/Turkey
Telephone:0322 3386060/3212

REFERENCES

1. Ascher PW: Laser trends in Minimally invasive Treatment: Atherosclerosis, Disk herniation J Clin Laser Med Surg 49–57,1991
2. Astrup J, Siesjö BK, Symon L: Thresholds in cerebral ischemia–the ischemic penumbra. Stroke 12:723–725,1981
3. Baskın DS, Hosobuchi Y, Grevel JC: Treatment of experimental stroke with opiate antagonists. Effect on neurological function infarct size and survive. J Neurosurg 64:99–103,1986
4. Beck OJ, Frank F: The use of Nd: YAG in neurosurgery Lasers Surg Med 5: 345–356,1985
5. Boggan JE, Edwards MSB, Davis RL, Bolger CA,Martin N: Comparison of the brain tissue response in rats to injury by argon and CO_2 lasers. Neurosurgery 11:609–616,1982
6. Braughler JM, Hall ED: Correlation of methylprednisolone levels in cat spinal cord with its effect on (Na+–K+) ATPase, lipid peroxidation and alpha motor neuron function. J Neurosurg 56:838–844, 1982
7. Capdeville C, Pruneau D, Allix M : Naloxane effect on the neurological deficit induced by forebrain ischemia in rats. Life Sci 38:437–442,1986
8. Cerullo LJ: Applications of lasers in Neurosurgery. New York: Year Book, 1988
9. Coles JC, Ahmed SN, Mehta HU: Role of free radical scayanger in protection of spinal cord during ischemia. Ann Thorac Surg 41:551–556,1986
10. Davis RJ, Bulkley GB, Traystman RJ: Role of oxygen free radicals in focal brain ischemia. Fed Proc 46: 2816–2819,1987
11. Ellis EF, Wrihgt KF Wei E: Cyclooxygenase products of

archidonic acid metabolism in cat cerebral cortex after experimental concussive brain injury. J Neurochem 37: 892–896,1981
12. Faden AI: Neuropeptides and stroke: Current status and potential application. Stroke 14:169–172,1983
13. Faden AI, Hallenbeck JM, Brown CQ: Treatment of experimental stroke: comparison of naloxane and TRH. Neurology 32:1083–1087,1982
14. Faden AI, Jacobs TP, Holaday JW: TRH improves neurologic recovery after spinal trauma in cats. N Engl J Med 305:1063–1067,1981
15. Faden AI, Jacobs TP, Smith MT,Holaday CW: Naloxone and dexamethasone treatments in experimental spinal injury. Neurology 33:673–678,1983
16. Fukuda N, Yoshiaki S, Nagawa Y: Behavioral and EEG alterations with brain stem compression and effect of TRH in chronic cats. Fol Pharm J 75:321–331,1979
17. Gaetani P: Ex vivo release of eicosanoid from human brain tissue: Its relevance in the development of brain edema. Neuroradiology 28: 853–858,1991
18. Holaday JW, D'Amato RJ: Naloxane and ischemic neurologic deficit in the gerbil: Is there an effect? Science 218:592–593,1982
19. Holaday JW, D'amato R, Faden AI: TRH improves cardiovascular function in experimental endotoxic and hemorrhagic shock. Science 213:216–218,1981
20. Holaday JW, Ruvio BA, Faden AI: TRH improves blood pressure and survival in endotoxic shock. Eur J Pharmacol 74:101–105,1981
21. Holaday JW, Tseng LF, Loh HH, Li CH: Thyrotropin releasing hormone antagonize β endorphin hypothermia and catalepsy. Life Sci 22 :1537–1544,1978
22. Jain KK: Lasers in neurosurgery a review. Lasers Surg Med 2: 217–230,1983
23. Kinuta Y, Kikuchi H, Ishikawa M, Kinmura M, Itokawa Y: Lipid peroxidation in focal ischemia. J Neurosurg 71:421–429,1989
24. Leslie JB,Watkins D: Eicosanoids in the central nervous system. J Neurosurg 67:659–668,1988
25. Lowry OH, Rosebrough NJ, Farr AL, Randal RJ: Protein measurement with the Folin Phenol Reagent. J Biol Chem 193:265–275,1951
26. Mayes PA: Metabolism of unsaturated fatty acids and eicosanoids. In Harper's biochemistry. Murry RK, Granner DK, Mayer PA, Redwell VW (eds), 21 st Appleton and lange, Middle East Edition. Libanon Ch 25 1988: 210–217
27. McCord JM, Oxygen–derived free radicals in postischemic tissue injury. N Engl J Med 312:159–163,1985
28. Millonig G: Advantages of a phospate buffer for O_5O_4 solutions and fixation. J Appl Phys 32: 1637,1961
29. Reading HW, Isbir T: Action of lithium on ATP ase in transmitter release from rat iris. Biochem Pharmacol 28:3471–3477, 1979
30. Reading HW, Isbir T: The role of Cation–Activated ATPases in Transmitter Release from Rat Iris. Q J Exp Physiol 65:105–116, 1980
31. Rosomoff HL, Carrol F: Effect of laser on brain and neoplasm Surg Forum 16: 431–433,1965
32. Roth EF Jr, Gilbert HS: The pyrogallol assay for superoxide dismutase: Absence of a glutathione artifact. Anal Biochem 137:5052,1984
33. Schettini A, Lippman R, Walsh EK: Attenuation of decompressive hypoperfusion and edema by superoxide dismutase. J Neurosurg 71:578–587,1989
34. Sun AY: The effect of lipoxidation on synaptosomal Na+–K+ ATPase isolated from the cerebral cortex of squirrel monkey. Biochem Biophys Acta 266:350–360,1972
35. Tiznada E, James HE, Kemper C: Experimental CO_2 laser brain lesions and intracranial dynamics: Part 1: Effect on intracranial pressure, central venous pressure, electroencephalography and gross pathology. Neurosurgery 16: 5–8,1985
36. Tiznada E, James HE, Moore S: Experimental carbon dioxide laser brain lesions and intracranial dynamics: Part 2:Effects on brain water content and its response to acute therapy. Neurosurgery 16:454–457,1985
37. Wei EP, Dietrich WD, Poulishhock JT: Functional morphological and metabolic abnormalities of the cerebral microcirculation after concussive brain injury in cats. Circ Res 46 :37–47,1980
38. Wei EP, Ellison MD, Kontos HA : Effects of oxygen radicals on cerebral arterioles. Am J Physiol 248 H :157–162,1985
39. Wei EP, Kontos HA, Dietrich WD : Inhibition by free radical scavengers and by cyclooxygenase inhibitors of pial arteriolar abnormalities from concussive brain injury in cats. Circ Res 48: 95–103,1981
40. Wei EP, Lamb RG, Kontos HA: Increased phospholipase C activity after experimental brain injury. J Neurosurg 56:695–698,1982
41. Weisinger RA, Fridovich I: Superoxide dismutase. Organelle specificity. J Biol Chem 248:3582–3592,1973
42. Yarborough GG: On the neuropharmacology of thyrotropin releasing hormone (TRH). Prog Neurobiol 12:294–312,1979