NEUROPHARMACOLOGY
Clinical Applications

Edited by

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Preface

Research applications of neuropharmacology to clinical problems has, in recent years, enjoyed a growing interest and has, as a result, been increasingly explored. This tact has taken ón a bidirectional effort through which neuropharmacological methodologies have been applied to investigate clinical problems in psychiatry and neurology, or basic mechanisms underlying such clinical problems have been investigated through more basic neuropharmacological models and methods. The results have served to increase our knowledge about clinical neuropharmacology.

The present volume was conceived as an overview of topics of clinical interest and concern that have been related to basic neuropharmacological concepts or techniques. These topics span a variety of areas of current interest including social deprivation, drug abuse, smoking behavior, memory dysfunction, the affective disorders, psychosis, and motor disturbances. In each instance the approach taken has been novel in that the directions through each subject have led to better understanding of the clinical entity through the neuropharmacological studies of the responses in question.

The present volume is not a textbook of clinical neuropharmacology. It is rather a source for the clinician to clarify areas of clinical interest through an understanding of the related neuropharmacodynamics. We, the editors hope that this volume will provide the reader with something new—clinically useful and conceptually clarified.

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Neuronal-Glial Metabolic Interactions In Stress

Leonid Pevzner

INTRODUCTION

Classically Hans Selye's concept of stress (Selye, 1952, 1957) has emphasized, first of all, nonspecific reactions common to all stress factors, or kinds of stress. This idea has turned out to be quite promising, and it was subsequently confirmed under many different stress conditions. As will be demonstrated below, metabolic responses of neurons and glia in some cases are rather similar notwithstanding differences in the stress conditions used.

At the same time, however, in *in vivo* experiments, nervous and hormonal influences, both direct and indirect, upon various structures of nerve tissue form a too complicated pattern to result in identical metabolic changes in all these structures. Therefore the nonspecific components of stress can be added by individual specificity not only of particular kinds of stress under various experimental conditions but also of particular types of cells within the nervous system.

It should be mentioned that there hardly is a method of separate analysis of neurons and glial cells which can at present be claimed free from sufficient pitfalls (*vide infra*). All these considerations should be kept in mind when comparing the data of different authors which in some cases are rather contradictory.

Nevertheless, neuron-glia metabolic interactions are worth considering even at the present-day, perhaps somewhat unconvincing, state of this essential neurobiological problem. Historically, it was the neuron which initially became an object of functional biochemical studies of the nervous system at the cellular level (Hydén, 1943, 1947, 1955). Later on, however, evidence has been obtained by various authors which has indicated that the whole biochemical basis for

nervous activity cannot be accounted for only by the metabolic properties of the neuron alone (for literature, see monographs by Hydén, 1972; Jakoubek, 1974; Pevzner, 1979a; Varon and Somjen, 1979).

A fruitful idea of the neuron-neuroglia metabolic unit put forward by Holger Hydén (1959, 1960, 1964) has stimulated a number of authors to deal with several aspects of neuronal-glial interactions including their interactions in stress.

MORPHOLOGICAL AND METHODOLOGICAL OUTLINES

In terms of histogenesis, both neurons and neuroglial cells originate from the same matrix cell, the medulloblast. Its initial differentiation leads to the formation of a neuroblast and a glioblast (as well as an ependymoblast). Final differentiation results in all types of neurons and glial cells, the latter consisting of two main classes, astrocytes and oligodendrogliocytes (Wechsler and Kleihues, 1968; Kuhlenbeck, 1970; Roots, 1978). It is worth indicating that evolutionarily the higher is the complexity of the whole organization of the animal, the greater is the number of glial cells relative to neurons, this ratio in mammalian brain becoming more than 10:1 (Hydén, 1972, Roots, 1978).

Whereas neurons are concentrated in some loci of the brain (cerebral and cerebellar cortex, basal ganglia, other nuclei of the brain or cerebellum), but absent in white matter or peripheral nerves, there are no loci in the central and peripheral nervous system free of glial cells. Their concentration may fluctuate there markedly depending upon localization but the total volume in the human cerebral cortex, for instance, which is occupied by astroglial and oligodendroglial cells may be roughly evaluated as about one third of the cortex tissue volume (Pope, 1978).

Both astrocytes and particularly oligodendrogliocytes have smaller sizes than neuronal bodies. The bodies and processes of glia form a network which surrounds every neuron and separates its body from brain capillaries (Peters et al., 1976). Such morphological interrelations make it extremely difficult for biochemists to separately analyze neuronal bodies and neuroglial cells.

At present, three chief approaches have been used for this purpose. The most recent and, perhaps, the most promising approach consists in obtaining large bulk of fractions enriched in neurons or, correspondingly, in glial cells. After initial disruption of brain tissue mechanically and/or enzymatically, a gradient ultracentrifugation is used which is based on different specific densities of neuronal bodies and glial cell bodies. There are many rather different schemes of this technique which result in enriched fractions with quite dissimilar degrees of purity, yield, morphological preservation of the cells, ratio of neurons and particular classes of glial cells as well as their viability and metabolic properties. Detailed description and critical evaluation of this approach can be found in

reviews by Rose (1969), Johnston and Roots (1972), Sellinger and Azcurra (1975), Poduslo and Norton (1975), and Varon and Somjen (1979). Along with a number of advantages, this approach possesses some shortcomings, among which two are the most important: contamination of each kind of cells and lack of regional, topochemical analysis of individual types of neurons. To the same approach, although with some reservations, a method of *in vitro* culture of individual cell lines may be added, comprehensive analysis of this method recently being done by Fedoroff and Hertz (1977).

The second approach consists in microdissection of individual, as a rule sufficiently large neuronal bodies and surrounding clumps of glial cells. The samples obtained are so minute that their biochemical analysis requires application of microchemical or even ultramicrochemical methods. This requirement itself can be considered as a disadvantage of the approach which requires unique equipment and poses a number of methodical difficulties. Besides, the sample of perineuronal neuroglia contains all non-neuronal elements of the nerve tissue such as axons, dendrites, microglial cells, brain capillaries, etc. Due to necessity of microsurgical manipulations, only the largest neurons are most often studied: spinal ganglia neurons, spinal cord motoneurons, Deiters' neurons of medulla vestibular nuclei, etc. At the same time, the possibility of comparing several classes of individual neurons as well as their perineuronal glia represents an undoubted advantage of this approach. Its principles, description of procedure and criticism are exposed in papers by Lowry (1955, 1962), Hydén (1955, 1960, 1964), Giacobini (1956, 1964), Rose (1968, 1969).

The third approach is quantitative cytochemistry, *i.e.*, analysis of individual neurons and glial cells, under visual control, within histological sections of the nerve tissue. Combination of microscopy with spectroscopy (Caspersson, 1950, 1955, 1979) or interferometry (Barer, 1956; Davies, 1958; Wied, 1966) as well as some other procedures (autoradiography, fluorescence, immune and enzymatic reactions, etc.) allows determinations of chemical composition and metabolic responses of various kinds of neurons and neuroglia. This approach is particularly suitable to deal with a unique heterogeneity of the nerve tissue. Besides, it preserves morphological interrelations among individual cell structures of the nervous system, without any mechanical disruption of the tissue. This advantage of the cytochemical approach is counterbalanced by a comparatively low specificity of cytochemical procedures for individual chemical substances as well as by possible error sources which may decrease markedly the preciseness of cytochemical analysis (Wied, 1966). Critical comparison of all three approaches, their principles and literature can be found in monograph by Pevzner (1979a).

Whereas the majority of data concerning chemical composition of neurons and glia have been obtained by means of the first approach (enriched fractions), metabolic changes in neurons and glial cells at various kinds of stress have been revealed as a rule with the aid of microchemical or cytochemical methods.

EFFECTS OF HYPOXIA

When animals are subjected to *in vivo* hypoxia, its effect by no means can be restricted by merely an oxygen deficiency. The stress-like nature of general hypoxia results in participation of a number of adaptational mechanisms such as blood circulation, lung ventilation, tissue metabolism, etc. Among these mechanisms a hypothermic mechanism is worth mentioning. Data obtained by Chetverikov's group not too well known to western neurochemists have shown that the hypobaric hypoxia in rats (as a result of exposition of the animals in a low pressure chamber) induces rather rapidly a sufficiently pronounced hypothermia. It is this hypothermia rather than the hypoxia alone which evokes a decrease in brain phospholipid turnover. The same hypoxia but with an artificial warming of the rats which prevents the hypothermia gives rise, on the one hand, to quite normal phospholipid turnover but, on the other hand, to a marked mortality of these animals (Gasteva et al., 1966).

The most systematic studies on effects of *in vitro* hypoxia upon neuronal and glial metabolism have been carried out by Yanagihara (1973, 1974, 1976, 1979). He has provided for careful analysis of rates of RNA and protein synthesis taking into account essential methodical factors such as disruption of cells in the course of enriched fraction preparation, uptake of precursors of macromolecular syntheses, activity of corresponding enzymes, effects of ions and specific inhibitors. Basing on these data Yanagihara demonstrated that *in vitro* hypoxia produced similar effects on neuronal and glial macromolecular synthesis. In other words, sensitivity to hypoxia did not differ markedly between the two cellular elements of the nervous system.

As expected from all the considerations discussed above, an *in vivo* hypoxia evoked metabolic responses rather different in neurons and in glial cells. Hydén's group compared cytochrome oxidase activity in the bodies of Deiters' neurons and in perineuronal tissue containing glial cells after their microdissection. Micromanometric determinations have shown that if the animals had been exposed 12 h in an atmosphere containing as little as 8 percent oxygen, the cytochrome oxidase activity increased in the neurons but did not change in the glial cells (Hydén and Lange, 1961; Hamberger and Hydén, 1963; Hydén, 1964). Thus, microdissectional approach has provided for evidence in favor of a higher resistance of glial metabolism to *in vivo* hypoxia than of neuronal one.

Similar conclusion has been made with the aid of enriched fraction approach. According to Albrecht and Smialek (1975), 30-minute exposition of rats to an atmosphere of 4 percent O_2 or 1.5-h exposition in a hypercapnic atmosphere inhibited *in vivo* incorporation of ^{75}Se-methionine into proteins both of neuronal and of glial enriched fractions of the brain hemispheres. This inhibition was much more persistent in neurons than in glia.

More complicated pattern of changes in precursor incorporation into neuronal and glial proteins has been revealed at *in vivo* hypoxia by Blomstrand

(1970). In his experiments rabbits were kept in an atmosphere of 8 percent O_2 for 3 or 12 h, then their cerebral cortex slides were incubated with ^{3}H-leucine. Its incorporation into protein of the slides was decreased after 3 but increased after 12 h of hypoxia. If from the slides enriched fractions were isolated, the effect of 3-h hypoxia turned out to be localized in glial fraction only, while that of 12-h was much more pronounced in neuronal bodies. If the same precursor was administered to the animals intravenously, its incorporation into neuronal and glial proteins was changed after 12-h hypoxia in the same way as after the incubation of slides with ^{3}H-leucine. In this case, after 3-h hypoxia, incorporation of the precursor in glial enriched fraction was also decreased but in the neurons was somewhat augmented (Blomstrand, 1970).

Several contradictions of the data mentioned above are perhaps due to the fact that the authors studied either a single kind of neuron (Deiters' neurons) or all the cells of the whole brain (enriched fractions of cerebral hemispheres). Meanwhile similar conditions of hypoxia can evoke different effects in various kinds of neurons whose sensitivity to the cessation of oxygen and glucose supply has been shown to markedly differ (Van Liere and Stickney, 1963).

Indeed, cytospectrophotometric determinations have revealed individual differences in RNA changes in various central neurons and their perineuronal glia under several conditions of *in vivo* hypoxia (Pevzner, 1971, 1972, 1979b; Brumberg and Pevzner, 1976). In sodium barbital-anaesthetized cats, hypoxic hypercapnic hypoxia was induced by means of connection of an exposed tracheal cannula with a closed 3.5-*l* air jar. Duration of such hypoxia was 1 h. It resulted in a marked decrease in RNA content in the cytoplasm of visual and motor cortex neurons as well as in their glial satellite cells. In auditory cortex, such RNA decrease was observed only in the perineuronal neuroglia while in cerebellum neither in Purkinje cells nor in the surrounding glia. Rather similar pattern of RNA changes, with the only difference of glial RNA decrease being absent in visual cortex but present in cerebellum, was evoked by ischemic hypoxia due to bilateral ligation of vertebrae arteries in anaesthetized cats for 1 h together with an interrupted occlusion of both common carotid arteries every 5 min with 5-min pauses. In rats, acute or long-term hypoxia in a low pressure chamber (240 mm Hg, simulated altitude 8700 m, for the acute experiments while 290 mm Hg, simulated altitude 7000 m, for chronic experiments) gave rise in cerebellum to RNA accumulation both in Purkinje cells and in their perineuronal glia while in spinal cord ventral horns, only in neurons. In mice, acute histotoxic hypoxia due to intraperitoneal KCN injection (10 mg/kg) brought about in 15 min an activation of M-form of lactate dehydrogenase in spinal cord motor neurons and spinal ganglia neurons without statistically significant changes in their perineuronal glia. In cerebellar and cerebral cortex neurons, there was an augmentation of H-form activity whereas in the glial cells adjacent to cerebellum Purkinje cells both H-form and M-form of lactate dehydrogenase were activated (Brumberg and Pevzner, 1976).

EFFECTS OF COOLING

Cooling is one of the most often used forms of stress. A great number of physiological data summarized by Mrosovsky (1971) and Hensel (1973) have presented an evidence in favor of direct involvement of various hypothalamus nuclei in an adaptation reaction to this kind of stress.

If laboratory albino rats raised in thermostatically controlled animal house were placed in a cold room at 2-4° C, the nuclear histone content per cell was increased in 24 h both in medial preoptic area and in supraoptic nucleus neurons (Krichevskaya et al., 1976). In glial cells there was a simultaneous decrease in the histone content in supraoptic nucleus while no changes in medial preoptic area. In the latter, a decrease in the histone content was observed in the whole neuron-neuroglia unit after 3-day exposure of the animals to the cold whereas in supraoptic nucleus the initial reciprocal changes were replaced by the inverse ones: a decrease of the neuronal and accumulation of the glial histones. After 15-day constant cooling, the content of neuronal and glial histones returned completely to the norm in the hypothalamus area studied (Krichevskaya et. al., 1976).

In the experiments described above, the stress seemed to be rather mild. Although laboratory rats are accustomed to live at a room temperature, living under conditions of as moderate cooling as 2-4° C hardly represents too severe stress for the given species. Therefore the metabolic response in hypothalamic structures was not too pronounced and disappeared as result of cold adaptation by a fortnight. Another pattern of metabolic response to a cooling was revealed in the case of much more severe cooling suggested by LeBlanc (1967). A modification of LeBlanc's scheme of cold adaptation consisted in that rats in individual cages were placed for 2 min in a cold room a -20° C, then kept for 5 min at 25° C, and then again cooled at -20° C for 2 min, this cycle being repeated 15 times (Filipchenko et al., 1978). As a result, the whole experiment lasted about 1.5 h, *i.e.*, twice as short as that in LeBlanc's work, and included a total of 30 min cooling. On the end of the cooling, the animals were returned to standard vivarium where they were kept up to 30 days. One hour on the cessation of the cooling, the RNA content per cell was shown cytospectrophotometrically to increase both in neurons and in perineuronal glia of medial preoptic area. This increase was observed also 2 days after the end of the cooling, with a return to the control value in another 3 days. More persistent increase in the RNA content was revealed in the neurons and perineuronal glia of mamillary bodies: it was found out as late as 5 and 15 days after the rats were returned to the animal house. It was only 30 days after the cessation of the cooling that the RNA content returned to the norm in the neurons and decreased somewhat lower than the norm in their glial satellite cells (Filipchenko et al., 1978).

EFFECT OF CONVULSIONS

Convulsions due to administration of various analeptics represent rather a convenient model of stress. Biochemical studies on this point at cellular level have dealt as a rule with neurons only. Parallel analysis of neurons and glial cells carried out by a few authors has shown a marked decrease in RNA and protein content both in motor neurons and perineuronal glial cells at the acute convulsions evoked by injections of picrotoxin (Rubinskaya, 1971) or Metrazol (pentamethylenetetrazol) (Pevzner, 1971; Pevzner and Saudargene, 1971). The degree of these changes and their stability depended much on whether the neurons investigated had been motor or sensory (Pevzner and Saudargene, 1971), secretory or nonsecretory (Schmidt and Zimmermann, 1978), cortical or spinal ones (Rubinskaya, 1971). But the whole pattern of RNA and protein reduction was rather similar in all cases. The same decrease in RNA content in neurons and perineuronal glia as result of a convulsive state was observed by Pevzner (1979c) even when the seizures were induced by hyperbaric hyperoxy rather than by any analeptics. Perhaps this similarity is a consequence of general changes in blood circulation, carbohydrate and energy metabolism shown during experimental status epilepticus by Plum's group (Plum et al., 1968; Duffy et al., 1975).

Much more individual was a dynamics of postconvulsive reparation. Thus, after cessation of Metrazol convulsions, the restoration of initial content of RNA and proteins occurred much quicker in perineuronal glial cells than in spinal motor neurons (Pevzner and Saudargene, 1971). In hyperoxia-induced convulsions which were more severe than Metrazol convulsions, the postconvulsive reparation was characterized by more pronounced and stable changes which in many cases proceeded parallely in neurons and in neuroglia (Pevzner, 1979c).

Metrazol-evoked convulsions resulted in quantitative changes in protein content only, as far as cytospectrophotometric evaluation can be relied on. In the course of postconvulsive restoration, however, there were also some qualitative changes in protein molecules. They were found out by parallel determinations of the total protein content and of the protein SH-group content (Pevzner and Saudargene, 1971). On cessation of convulsions, the relative SH-group content (per mass unit of total protein) increased, this augmentation being absent in spinal motor neurons and their glia but present in spinal ganglia neurons and to a greater degree in their glial satellite cells.

EFFECT OF FOOT-SHOCK

This stress factor is also used quite often in studies on changes of metabolism in the nervous system under effects of stress. These changes at the level of the whole brain are exposed and critically discussed in a comprehensive monograph

by Jakoubek (1974). As to comparison of stress-induced metabolic responses in neurons and in neuroglia, the foot-shock has been applied only in single works.

Short-term foot-shock in rats has been shown to bring about reciprocal changes in RNA content: increase in spinal cord motor neurons but decrease in their perineuronal neuroglia, these changes being detected as soon as 5 min after beginning of the foot-shock (Pevzner, 1971). More prolonged foot-shock (20 min) resulted in a return of the neuronal and glial RNA content to the control level. At last, 60-min foot-shock gave rise to a pronounced reduction of RNA content both in the motor neurons and in adjacent glial cells. On cessation of the foot-shock, restoration of the control value of RNA content, like in the case of postconvulsive reparation (see above), was completed considerably sooner in the glial cells than in the motor neurons.

Since the foot-shock represents a kind of a most intensive sensory stimulation, it seemed that the most pronounced metabolic response should be revealed in sensory neurons. Meanwhile, in the whole course of 60-min foot-shock in rats there were no changes in the cytoplasmic RNA content in the spinal ganglia neurons (Pevzner, 1979a). In the period of a rest after the end of the foot-shock, the RNA content increased 4 h on cessation of the stress but completely returned to norm afterwards. It is not unreasonable to suggest that the macromolecular changes in the neuronal body take place mainly as a metabolic response to a synaptic multi-step stimulation rather than to a direct excitation of a sensory neuron through its peripheral receptors (Pevzner, 1979a).

An interesting kind of the foot-shock stress, anticipation stress, has been analyzed by Jakoubek (1974). Rats were placed in a cage with an electrical grid floor and a foot-shock was given to the animals after a waiting period of 45 min. This trial was repeated daily for 7 days, the animals were killed after 7 trials.

Biochemical analysis of the rats after 7 daily anticipation stress trials has shown that such an anticipation of a painful stimulation can alter essentially active transport of precursors into the brain tissue and biosynthesis of macromolecules from these precursors (Jakoubek, 1974).

Comparison of a metabolic response of neurons and of glial cells to the anticipation stress has revealed a number of intercellular differences (Jakoubek et al., 1979). At once after the 7th trial of the anticipation stress there was an augmentation of the cytoplasmic RNA content in spinal cord motor neurons while no changes were found out in the adjacent glial cells. A part of the animals were administered with a tranquilizer diazepam (10 mg/kg), on the 8th day of the experiment. Forty minutes later, the rats were placed into the same grid floor cage and killed after the 45-min waiting. Diazepam turned out to prevent any change in the neuronal RNA content. At the same time, an increase in glial RNA content was observed in the animals injected with diazepam (Jakoubek et al., 1979).

EFFECT OF RESTRAINT

Restraint, fixation of the animal to prevent any free movement is rather severe form of stress, so-called immobilization stress. However, neuron-glia interrelations have been studied only in experiments by Brumberg and her co-authors who applied a milder condition of restraint. Experimental animals, mice (Brumberg, 1969; Brumberg and Pevzner, 1972) and rats (Brumberg et al., 1972) were placed in individual cages which restrained movements of the animals but did not produce actual immobilization. As a result, such experiment could last two and even three weeks; it is only in the latter case that a discoordination, light paresis of hind legs and a loss of body weight were revealed. Cytospectrophotometric determinations have demonstrated no changes in the cytoplasmic RNA content in spinal cord motor neurons and spinal ganglia neurons as well as in the bodies of perineuronal glial cells of spinal cord ventral horns by the end of 3-week restraint. In neuroglia of spinal ganglia there was a marked reduction of the RNA content. After such prolonged hypokinesia, free motor activity of these mice outside the cages gave rise rapidly to a total decrease in RNA content both in the neurons and in the adjacent glial cells of the spinal cord and spinal ganglia (Brumberg and Pevzner, 1972). Subsequent return of the glial RNA to the control level, like in the cases of foot-shock or several kinds of convulsions (*vide supra*), was achieved more rapidly than that of the neuronal RNA. At the same time, as late as 3 days after the end of the hypokinesia, when all the symptoms of it completely disappeared, a normalization of the neuronal RNA content was accompanied by a secondary, delayed decrease in the content of glial RNA.

Still milder and shorter (for 2 weeks) hypokinesia in rats which had not resulted in any visible motor disturbances brought about different metabolic responses in spinal cord cells depending on their localization. In the lumbar enlargement of which motor neurons are responsible for hind leg muscular activity a marked increase was observed in the RNA content of the motor neurons while a decrease in that of perineuronal glia. In the cervical enlargement of the spinal cord no statistically significant changes were detected in the same animals. It is interesting that if this hypokinesia was combined with a moderate hypoxic hypoxia (the individual cages with animals were kept for two weeks in a low pressure chamber), the content of neuronal RNA remained normal or augmented in the cervical or lumbar intumescence resp. while the content of glial RNA markedly increased in both intumescences (Brumberg et al., 1972).

EFFECT OF A FORCED MUSCULAR ACTIVITY

In a series of works by Brumberg, adult male mice were put into a swimming pool for 3-4 h (Brumberg, 1968, 1969; Brumberg and Pevzner, 1972). According

to her cytospectrophotometric data, such a forced muscular activity induced an accumulation of cytoplasmic RNA in spinal cord motor neurons and a temporary decrease of cytoplasmic RNA in spinal ganglia. These changes in neurons were accompanied by no statistically significant alterations in glial RNA content. Subsequent rest of the animals after the cessation of the swimming was characterized by a return of the augmented RNA content in motor neurons to the norm while by a parallel decrease in the glial RNA.

Much more severe stress was achieved through swimming in experiments by Geinisman (1971, 1972). He was dealing with rats made to swim with an attached load which amounted to 1/11 of their body weight. This resulted in the animals beginning usually to submerge as soon as after 50 min of the swimming. Therefore the whole experiment lasted only 40 min. In the large motor neurons of the lumbal spinal cord intumescence, the content of cytoplasmic RNA somewhat increased while in the small motor neurons decreased by the end of the 40-min swimming. The content of glial RNA decreased, the change being localized only in perineuronal neuroglia rather than in the glial cells characterized by no visible contact with spinal motor neurons (Geinisman, 1971, 1972).

Another kind of a forced muscular activity was chosen by Tiplady et al. (1974): rats were running for one hour in the wheel. This gave rise to an accumulation of RNA both in nuclei and in the cytoplasm of pyramidal neurons of the motor area of cerebral cortex while no statistically significant changes in the RNA content were detected in perineuronal glial cells. It is interesting that the content of nuclear or cytoplasmic RNA in the motor neurons of the lumbar intumescence of the spinal cord, as well as in their glial satellite cells, remained unchanged in the same animals (Tiplady et al., 1974).

EFFECT OF ADRENALECTOMY

In the course of analysis of stress mechanisms, adrenalectomy is often used as one of the most efficient experimental approaches. Strangely enough, this approach was applied for studies on neuron-neuroglia metabolic interrelations only in a single paper.

Male rats were adrenalectomized under ether anaesthesia. They subsequently received normal food *ad libitum* while drinking water contained 1 percent NaCl. In cerebellum Purkinje cells as well as in spinal cord motor neurons, at the fourth day after the operation, the cytoplasmic RNA content was decreased. This decrease hardly could be considered specific because it persisted in a group of adrenalectomized rats administered daily with hydrocortisone. In perineuronal neuroglial cells the content of RNA remained constant in all cases. Quite opposite pattern appeared in hypothalamus, a brain area more specifically involved in a whole response to stress (hypothalamo-pituitary-adrenal system). Whereas no RNA alterations were revealed in hypothalamus supraoptic neurons