Localized Effects of Naloxone on Local Cerebral Glucose Utilization in Rat Cerebral Nuclei with Met-Enkephalinergic Neurons

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Abstract—The alterations of local glucose utilization in 101 cerebral nuclei following the subcutaneous administration of the specific opioid antagonist naloxone were measured using the quantitative autoradiographic 14C-deoxy-D-glucose technique in conscious rats. Met5-enkephalin-like immunoreactivity (MELI) and ME receptor binding (MERB) levels in 82 cerebral nuclei were assayed quantitatively by microdensitometry of fluorescence micrographs and autoradiographs of the brain slices. Naloxone administration significantly reduced glucose utilization rate in 18 lower brainstem nuclei including the n. tractus solitarii, n. dorsalis nervi vagi, substantia grisea centralis, n. parabrachialis dorsalis and ventralis, and n. interpeduncularis. These nuclei contained ME perikarya with high levels of MELI and MERB. However, naloxone did not alter glucose utilization of other lower brainstem nuclei containing ME neurons and all thalamic, epithalamic, hypothalamic and limbic nuclei with ME perikarya. The distribution and magnitude of the neuronal response of cerebral nuclei to naloxone were apparently not related to the distributions of ME neurons. The present study offers direct evidence for the selective action of naloxone per se in some lower brainstem nuclei with ME perikarya.

Naloxone has been utilized as a specific opioid antagonist for clarifying analgesic and other pharmacological actions of opioid agonists and also detecting the development of physical dependence on these agents. Furthermore, for characterizing opioid neurons extensively distributed throughout the brain (1-4), naloxone becomes an indispensable tool for clarifying major roles for opioid neurons in brain function: pain pathways (5-8), other physiological roles of opioid neurons on cerebral mechanisms of baroreceptor reflex (4, 9-11), blood pressure (12), shock-induced hypotension (13-15), ischemic neurologic deficits (16, 17), stress (18), learning and memory process (19, 20), feeding and drinking (21-22), and involvement of opioid neurons in actions of pharmacological agents like phenoxybenzamine (23), diazepam (24), meprobamate (24), ethanol and pentobarbital (25).

However, some conflicting results with the use of naloxone are known when the opioid neurons are activated (26-28) and when opioids were pretreated (8, 29-32). The autoradiographic 2-deoxy-D-[14C]-glucose (14C-DG) method has been employed in the present studies to localize cerebral nuclei in which functional activity is altered by blockade of the opioid receptors with naloxone. The autoradiographic 14C-DG method measures the rates of glucose utilization simultaneously in all of the cerebral nuclei in conscious rats (33). This method has been widely used to study function-related alterations in local cerebral glucose utilization under many experimental conditions (34).

Materials and Methods
The experiments were performed on male Wistar (Kyoto strain) rats when they reached...
the age of 20 weeks. For injection of \(^{14}\)C-DG, a polyethylene catheter was implanted into the carotid artery 3 days previously. The conscious, resting animals were injected intra-arterially with 165 \(\mu\)Ci/kg of \(^{14}\)C-DG (homogenously labelled, specific activity 326 mCi/m mole; New England Nuclear, Boston) and sacrificed by decapitation 45 min later, when \(^{14}\)C-DG-phosphate levels in the brain tissues reached a plateau (33). The brains were removed and processed for autoradiography as described previously (33, 35–37). Naloxone (10 mg/kg, s.c.) was administered immediately before the intra-arterial injection of \(^{14}\)C-DG. From each frozen brain, about 110 coronal sections (100 \(\mu\)m) were cut serially, mounted on glass cover slips, and dried on a hot plate at 60°C. Autoradiographs were prepared in X-ray cassettes by exposing the dried sections to Kodak XR-1 films for a fixed period of 20 days. \(^{14}\)C-Methylmethacrylate standards including a blank and a series of 7 different \(^{14}\)C-levels were simultaneously placed in the cassette. The silver granule density of the autoradiograph was measured with a microdensitometer (Gamma Scientific Corp.) in areas of 200 \(\mu\)m diameter using simultaneously developed autoradiographs of \(^{14}\)C-methylmethacrylate as references. For calculating the glucose utilization rate, the arterial blood was collected through the implanted carotid catheter to measure glucose and \(^{14}\)C-DG concentrations in the plasma immediately before and at 5, 10, 20, and 45 min after the injection of \(^{14}\)C-DG. Plasma glucose was assayed by the glucose oxidase method (Roche kit). For calculating the rate of glucose utilization (GUR) in 101 cerebral nuclei and areas, a modified equation (35) based on that of Sokoloff et al. (1977) (33) was used. In 82 cerebral nuclei and areas, both met-enkephalin (ME)-like immunoreactivity and its receptor binding (MERB) levels were measured quantitatively by autoradiograms prepared by using immunohistofluorescence antibody and by \(^{3}\)H-ME, respectively, as described previously (38–38). Anti-ME rabbit sera were not cross-reactive (<0.2%) with leu-enkephalin, ME-Arg-Arg, ME-Lys-Lys, ME-Lys-Arg, and slightly cross-reactive with ME-Arg (4.6%), ME-Lys (4.3%) and \(\beta\)-endorphin (6.5%).

Brain anatomy and terminology were as described by König and Klippel (1970) (39) and Palkovits and Jacobowitz (1974) (34). Aortic blood pressure was measured in some conscious animals with a pressure transducer (Nihon Kohden MPU 0.5) through the carotid catheter. Heart rates were triggered through pulses of aortic blood pressures. For statistical analysis, the Student’s t-test was employed.

Results

Glucose utilization rate in cerebral nuclei: As summarized in Table 1, GUR varies widely throughout the brain. Among 101 cerebral nuclei and areas examined, high GUR was detected in the nucleus (n.) olivaris superior, n. interpeduncularis, n. corporis mamillaris medialis and lateralis, n. caudalis, tuberculum olfactorium, and cortex cingularis and frontalis, probably the metabolically most active structures in the brain. These findings are in accordance with the previous ones (35, 37, 40).

ME neurons in cerebral nuclei: Both MELI and MERB levels were relatively high in the n. tractus solitarii (NTS), n. parabrachialis, n. interpeduncularis, some hypothalamic nuclei, n. amygdaloideus centralis, most stria terminal nuclei, and n. accumbens septi. These nuclei contained ME perikarya and had MELI and MERB levels of more than 400 and 300 pmole/g of the tissue. The present findings are comparable to those of previous studies on the rat brain based on immunohistochemistry (3, 20, 36, 37, 41). The nuclei with the presence of rich ME neurons did not correspond to the ones with high levels of GUR.

Effects of naloxone on gross behavior, aortic blood pressure and heart rate: Naloxone at the dose of 10 mg/kg s. c. did not alter gross behaviors, aortic blood pressure (initial 114±5 mmHg versus 118±8 mmHg 0.5 hr later, n=6) and heart rate (302±18 bpm versus 311±26 bpm) of conscious animals in the resting state for a period up to 5 hr.

Effects of naloxone on glucose utilization rate in cerebral nuclei: Among 101 cerebral nuclei examined, naloxone significantly decreased GUR in 18 nuclei (Table I). The
inhibitory effect of naloxone was topographically limited on some nuclei in the brainstem. These affected nuclei which contained ME perikarya were the n. commissuralis, caudal part of the NTS, area postrema, n. ambiguus, n. dorsalis nervi vagi, n. parabrachialis dorsalis and ventralis, and n. interpeduncularis. Naloxone also decreased GUR in the n. raphe obscurus and substantia grisea centralis, the areas containing ME axon and fiber. Naloxone decreased GUR in the n. olivaris superior where ME neurons did not exist. On the other hand, naloxone did not change GUR in the lower brainstem nuclei with ME perikarya: the n. tractus spinalis nervi trigemini, n. originis nervi hypoglossi and most of brainstem reticular nuclei including n. tegmenti dorsalis and ventralis. Furthermore, naloxone did not significantly alter GUR in thalamic, epithalamic, hypothalamic and limbic nuclei containing rich ME neurons (Table I, Fig. 1).

Discussion

The present investigation demonstrates that naloxone when applied systemically decreases GUR in a limited number of the lower brainstem nuclei with the presence of ME perikarya. Most of the ME neurons in thalamic, epithalamic, hypothalamic and limbic nuclei were free from the action of naloxone. Our findings offer direct support for the notion that naloxone s.c. does not act on all ME containing nuclei, but acts on limited kinds of lower brainstem nuclei among those containing ME perikarya. The heterogeneity of multiple opioid receptors has been substantiated by receptor binding studies. Naloxone has high affinity to $\mu$ sites and low affinity to $\delta$ and $\epsilon$ sites (41). It is well recognized that cerebral distribution of $[^3H]_n$aloxone binding sites directly correlate with those of ME (42) and leu-enkephalin (43). $[^3H]_n$aloxone preferably binds with striate, interpeduncular nucleus, central nucleus of amygdala, accumbens nucleus and central gray in rat brains (44). However, all these studies have been made with rat brain slices in vitro.

A similar observation of reduced oxygen consumption in the pons and hypothalamus has been reported following intravenous administration of the opioid antagonist naltrexone to anesthetized cats (45). However, the species difference in response to opiates makes comparison of both studies difficult. Opiates are depressant in rats and excitatory in cats. Difference in the inhibitory
Table 1. Effects of naloxone on local cerebral glucose utilization of cerebral nuclei containing met-enkephalinergic neurons

| Structure                                         | Local cerebral glucose utilization (pmol/100 g/min) | Met-enkephalinergic neurons |
|--------------------------------------------------|--------------------------------------------------|-----------------------------|
|                                                  | Untreated control (8) | Naloxone treated (8) | % change | Type of distribution | Met-enkephalin-like immunoreactivity (pmol/g) (8) | Met-enkephalin receptor binding (pmol/g) (8) |
| Rhombencephalon and mesencephalon                 |                                                  |                            |          |                     |                                               |                                        |
| N. intercalatus                                  | 75±1.5                                          | 74±1.7                     | -8       | A, F                | 72±4.5                                        | 42±4.5                                    |
| N. commissuralis                                 | 96±1.9                                          | 88±1.9**                   | -8       | P                   | 331±12.7                                      | 242±24.6                                  |
| Area postrema                                     | 90±1.7                                          | 81±2.4**                   | -10      | P                   | 136±6.8                                       | 74±8.4                                    |
| N. tractus solitarii (caudal)                     | 107±1.4                                         | 98±1.5**                   | -8       | P                   | 633±17.8                                      | 418±42.2                                  |
| N. tractus solitarii (rostral)                    | 92±1.3                                          | 90±1.3                     |          |                     |                                               |                                        |
| N. ambiguus                                      | 91±1.3                                          | 84±1.4*                    | -8       | P, A, F             | 251±14.2                                      | 145±18.4                                  |
| N. originis nervi hypoglossi                     | 66±1.7                                          | 65±2.0                     |          | P                   | 211±19.2                                      | 148±18.7                                  |
| N. dorsalis nervi vagi                           | 91±1.5                                          | 80±1.7***                  | -12      | P                   | 248±15.5                                      | 132±16.4                                  |
| N. olivaris superior                             | 133±1.9                                         | 125±1.8*                   | -6       |                     |                                               |                                        |
| N. olivaris inferior                             | 81±1.5                                          | 77±1.9                     |          |                     |                                               |                                        |
| Locus coerules                                   | 67±1.4                                          | 62±1.4*                    | -7       |                     |                                               |                                        |
| Sublocus coerules                                | 59±1.8                                          | 59±1.0                     |          |                     |                                               |                                        |
| N. tractus spinalis n. trigemini                 | 91±1.9                                          | 90±1.2                     |          | P                   | 220±11.8                                      | 149±20.4                                  |
| N. originis n. trigemini                         | 91±1.8                                          | 89±1.9                     |          |                     |                                               |                                        |
| N. principalis n. trigemini                      | 94±1.9                                          | 89±1.5*                    | -5       |                     |                                               |                                        |
| N. tractus mesencephalicus n. trigemini          | 95±1.4                                          | 90±1.3*                    | -5       |                     |                                               |                                        |
| N. parabrachialis dorsalis                       | 77±1.6                                          | 71±1.7*                    | -8       | P                   | 996±57.1                                      | 629±58.3                                  |
| N. parabrachialis ventralis                      | 76±1.3                                          | 70±1.8*                    | -8       | P                   | 902±22.1                                      | 565±48.8                                  |
| Pedunculus cerebellaris superior                 | 76±1.8                                          | 75±1.3                     |          |                     |                                               |                                        |
| N. fastigii                                      | 100±2.0                                         | 94±1.9*                    | -6       |                     |                                               |                                        |
| N. interpeduncularis                             | 126±1.7                                         | 119±1.9*                   | -6       | P                   | 402±25.4                                      | 359±42.6                                  |
| Substantia nigra pars compacta                   | 76±1.7                                          | 75±1.7                     |          |                     |                                               |                                        |
| Substantia grisea centralis                      | 86±1.0                                          | 76±1.5****                 | -12      | A, F                | 381±19.4                                      | 152±15.8                                  |
| Thalamus and epithalamus                         |                                                  |                            |          |                     |                                               |                                        |
| N. paramedianus                                  | 106±1.3                                         | 105±1.4                    |          | P                   | 91±5.7                                        | 33±3.8                                    |
| N. centromedianus                                | 106±1.7                                         | 106±1.3                    |          | P, A                | 66±4.2                                        | 30±4.6                                    |
| N. dorso medialis                                | 106±2.3                                         | 106±1.8                    |          | P, A                | 86±4.4                                        | 37±3.2                                    |
| N. ventro medialis                               | 105±2.0                                         | 104±1.7                    |          | P                   | 67±4.4                                        | 27±3.3                                    |
| Structure                          | Local cerebral glucose utilization (μmol/100 g/min) | Met-enkephalinergic neurons |
|-----------------------------------|-----------------------------------------------------|-----------------------------|
|                                  | Untreated control (8) | Naloxone treated (8) | % change | Type of distribution | Met-enkephalin-like immunoreactivity (pmol/g) (8) | Met-enkephalin receptor binding (pmol/g) (8) |
| N. habenulae medialis (NHM)       | 101±1.4 | 100±1.9 |                  | P          | 126±5.2             | 71±6.9                        |
| N. habenulae lateralis (NHL)      | 109±1.8 | 109±2.0 |                  | P          | 121±5.2             | 66±7.2                        |
| **Formatio reticularis**          |          |          |                  |            |                      |                              |
| N. raphe obscurus (NROb)          | 71±1.3   | 66±1.5*  | -7               | F          | 203±6.4             | 105±16.4                     |
| N. raphe pallidus                 | 75±1.7   | 72±1.4   |                  | F          | 178±5.6             | 97±13.2                       |
| N. raphe magnus (NRMg)            | 75±1.2   | 73±1.4   |                  | F          | 223±8.1             | 105±14.5                     |
| N. reticularis paragigantocellularis (NRPG) | 72±2.0 | 70±2.1 |                  | F          | 87±5.1              | 31±3.4                       |
| N. reticularis pontis caudalis    | 74±1.9   | 74±2.2   |                  | F          | 213±4.9             | 111±15.1                     |
| N. reticularis pontis oralis      | 76±1.4   | 77±1.4   |                  | F          | 213±4.9             | 111±15.1                     |
| N. reticulotegmentalis pontis     | 78±1.8   | 70±1.4** | -10              | P, F       | 712±11.8            | 348±37.9                     |
| N. ruber mesencephali (NRuM)      | 70±0.9   | 69±1.3   |                  | F          | 54±4.8              | 31±3.0                       |
| N. reticularis parvovalcellularis (NRPC) | 71±1.7 | 71±2.1 |                  | P, F       | 87±4.4              | 52±5.6                       |
| N. reticularis lateralis (NRL)    | 77±1.5   | 77±14    |                  | P          | 74±3.3              | 39±4.4                       |
| N. cuneiformis                    | 73±1.9   | 74±2.4   |                  | P          | 113±4.6             | 44±5.2                       |
| N. tegmentalis pedunculopontinus (NTPP) | 106±1.4 | 100±1.7* | -6               | P, F       | 85±4.8              | 59±4.7                       |
| N. reticularis medialis (NRM)     | 70±1.3   | 71±1.5   |                  | P, F       | 85±4.8              | 59±4.7                       |
| N. reticularis dorsalis (NRD)     | 69±1.7   | 67±1.8   |                  | P, F       | 47±3.3              | 22±3.0                       |
| Substantia reticularis mesencephali | 78±1.8 | 75±1.3 |                  | A, F       | 71±3.1              | 28±4.5                       |
| N. intralaminalis                 | 80±1.9   | 79±1.4   |                  | ~          | ~                   | ~                            |
| N. reticularis thalami            | 74±1.3   | 74±1.5   |                  | ~          | ~                   | ~                            |
Table 1. (continued)

| Structure                        | Local cerebral glucose utilization (µmol/100 g/min) | Met-enkephalinergic neurons |
|----------------------------------|---------------------------------------------------|----------------------------|
|                                  |Untreated control (B) | Naloxone treated (B) | % change | Type of distribution | Met-enkephalin-like immunoreactivity (pmol/g) (B) | Met-enkephalin receptor binding (pmol/g) (B) |
|----------------------------------|----------------------|----------------------|-----------|----------------------|-----------------------------------------------|-----------------------------------------------|
| Hypothalamus                     |                      |                      |           |                      |                                               |                                               |
| N. posterior hypothalami         | (NPH)                | 102±1.7              | 103±1.3   | P, F                 | 86±4.2                                        | 49±4.2                                        |
| N. corporis mammilaris medialis  | (HMM)                | 129±1.0              | 130±1.5   | P                     | 48±2.5                                        | 32±2.9                                        |
| N. corporis mammilaris lateralis | (NML)                | 129±1.5              | 128±1.9   | P                     | 50±3.9                                        | 37±3.8                                        |
| N. ventromedialis                | (NVM)                | 73±1.8               | 72±1.7    | P                     | 93±3.6                                        | 60±5.8                                        |
| N. dorsomedialis                 | (NDM)                | 79±1.5               | 78±1.3    | P                     | 70±3.4                                        | 52±4.5                                        |
| Area lateralis hypothalami       | (ALH)                | 84±1.8               | 86±1.5    | P                     | 124±4.7                                       | 81±7.3                                        |
| Area anterior hypothalami        | (AAH)                | 69±1.3               | 69±1.7    | P                     | 141±4.6                                       | 62±6.9                                        |
| N. suprachiasmaticus             | (NSC)                | 103±1.7              | 100±1.9   | P                     | 488±25.8                                      | 231±28.4                                      |
| N. paraventricularis             | (NPA)                | 108±1.9              | 108±1.5   | P                     | 424±23.9                                      | 246±26.2                                      |
| N. suprachiasmaticus             | (NSC)                | 79±1.7               | 80±1.4    | P                     | 513±24.9                                      | 236±28.5                                      |
| N. periventricularis             | (NPV)                | 74±1.7               | 75±1.3    | P                     | 752±21.0                                      | 349±32.6                                      |
| N. arcuatus                      | (NAR)                | 78±1.7               | 77±1.0    | P, F                  | 528±27.9                                      | 307±28.9                                      |
| Median eminence                  |                      | 76±1.5               | 76±1.7    | F                     |                                               |                                               |
| Infundibulum                     |                      | 79±1.4               | 78±1.3    | F                     |                                               |                                               |
| Area preoptica medialis          |                      | 83±1.9               | 83±1.9    | F                     |                                               |                                               |
| Area preoptica lateralis         |                      | 74±1.8               | 75±1.8    | F                     |                                               |                                               |
| Fasciculus medialis telencephali |                      | 80±2.3               | 79±1.7    | A, F                  | 81±5.8                                        | 44±3.9                                        |
| (caudal)                         |                      |                      |           |                      |                                               |                                               |
| Fasciculus medialis telencephali |                      | 87±1.8               | 86±1.5    | A, F                  | 65±3.6                                        | 22±3.1                                        |
| (rostral)                        |                      |                      |           |                      |                                               |                                               |
| Fasciculus longitudinalis dorsalis|                     | 74±1.6               | 74±0.7    | A, F                  | 152±5.5                                       | 63±4.8                                        |
| Forel H                          |                      | 82±1.9               | 81±1.7    | A, F                  | 118±5.4                                       | 42±3.7                                        |
| Zona incerta                     |                      | 74±1.8               | 74±2.7    | F                     | 44±4.0                                        | 41±3.1                                        |
| Nuclei telencephali              |                      |                      |           |                      |                                               |                                               |
| N. amygdaloideus lateralis       | (NAml)               | 62±1.9               | 61±1.7    | P, F                  | 88±4.8                                        | 44±3.8                                        |
| N. amygdaloideus centralis       | (NAmc)               | 59±1.5               | 60±2.3    | P, F                  | 655±28.9                                      | 416±40.7                                      |
| N. amygdaloideus medialis        | (NAmm)               | 74±1.7               | 73±1.8    | P, F                  | 109±4.6                                       | 66±5.8                                        |
| N. amygdaloideus intercalatus    | (NAmi)               | 81±1.0               | 80±1.4    | A, F                  | 56±3.7                                        | 38±4.3                                        |
| N. amygdaloideus basalis pars lateralis| | 81±1.4               | 81±1.7    | P                     | 43±4.0                                        | 26±2.7                                        |
| Structure | Local cerebral glucose utilization (μmol/100 g/min) | Met-enkephalinergic neurons |
|-----------|---------------------------------|-----------------------------|
|           | Untreated control (8) | Naloxone treated (8) | % change | Type of distribution | Met-enkephalin-like immunoreactivity (pmol/g) (8) | Met-enkephalin receptor/binding (pmol/g) (8) |
| N. amygdaloideus basalis pars medialis | 76±1.7 | 75±1.9 | P | 43±3.3 | 25±3.1 |
| N. amygdaloideus corticalis | 66±1.3 | 66±1.7 | P, F | 47±3.2 | 24±2.8 |
| Area amygdaloidea anterior (AAmA) | 88±1.4 | 87±1.3 | P, F | 41±4.0 | 24±2.7 |
| N. tractus olfactorii lateralis | 101±1.3 | 101±1.5 | F | 124±7.6 | 62±7.3 |
| N. proprius striae terminalis (NPST) | 77±1.4 | 77±1.2 | P, F | 196±32.9 | 322±30.4 |
| N. interstitialis striae terminalis dorsalis (STD) | 76±1.7 | 75±1.3 | P, F | 615±36.1 | 341±28.6 |
| N. interstitialis striae terminalis ventralis | 74±1.3 | 73±1.9 | P, F | 559±22.8 | 274±28.3 |
| N. interstitialis striae terminalis medullaris | 88±1.6 | 88±1.8 | P, F | 567±25.7 | 297±27.9 |
| N. dorsalis septi (NDS) | 74±1.7 | 75±1.7 | P | 66±3.7 | 29±2.3 |
| N. medialis septi (NMS) | 74±1.5 | 73±1.8 | P | 50±3.0 | 24±2.8 |
| N. lateralis septi | 75±1.9 | 74±1.0 | P | 82±4.3 | 46±5.2 |
| N. intermedium septi | 73±1.6 | 74±1.9 | P, F | 48±2.2 | 26±3.1 |
| N. accumbens septi (NAS) | 94±1.3 | 94±1.5 | P, F | 821±39.2 | 426±42.9 |
| N. caudatus (NC) | 128±1.2 | 124±2.2 | P, A, F | 125±5.4 | 109±8.4 |
| Tuberculum olfactorium (TO) | 128±1.7 | 129±1.9 | P, F | 100±4.4 | 52±4.7 |
| Cortex cerebri | | | | | | |
| Hippocampus dorsalis | 96±1.6 | 96±2.5 | ~ | ~ | ~ |
| Hippocampus ventralis | 97±1.7 | 98±1.4 | ~ | ~ | ~ |
| Subiculum | 96±1.3 | 95±1.7 | ~ | ~ | ~ |
| Cortex entorhinalis (CXE) | 103±1.3 | 103±1.6 | P, F | 54±3.8 | 33±3.8 |
| Cortex piriformis (CXP) | 108±1.4 | 108±1.8 | P, F | 56±3.6 | 40±3.2 |
| Cortex cingularis (CXC) | 122±1.9 | 123±2.0 | P, F | 69±3.2 | 41±4.5 |
| Cortex frontalis | 125±1.7 | 125±1.4 | P, F | 60±3.3 | 45±3.9 |

Data are means±S.E.M. for the number of animals shown in parenthesis. *P<0.05, **P<0.02, ***P<0.001, compared with corresponding untreated controls. A=MELI containing axon, F=MELI containing fiber, P=MELI containing perikarya, ~<20 pmol/g.
effect on the hypothalamus may be due to pharmacokinetic disposition of naltrexone i.v. as compared to naloxone s.c. As for the selective action of naloxone in the lower brainstem nuclei, naloxone is known to reverse the circulatory collapse induced by hemorrhagic and endotoxin shocks (13, 14), and spinal traumatic shock (15), probably acting through the circulatory and respiratory centers in the medulla oblongata. Shock-induced hypotension elicits the release of the endogenous opioid in the lower brainstem nuclei, since various hypotensive treatments of SHR produce the increases in GUR, MELI and MERB levels in these NTS and related medullary nuclei (9, 36, 37, 46).

The present investigation with naloxone indicates that naloxone itself acts to decrease GUR in limited nuclei of the brainstem area. These findings taken together indicates that some caution should be taken regarding the interpretation that naloxone itself is pharmacologically rather inert. These will explain the complicated responses to naloxone when opioid neurons are excited (26–28). GUR in the suprabulbar nuclei containing ME perikarya is not altered with naloxone. Thus, the action of naloxone in cerebral nuclei does not correlate well with the high concentration of MELI and MERB located there. The present regional analysis indicates that naloxone preferentially affects some of the lower brainstem nuclei, suggesting that opioids have a greater role in regulating activity in these regions than elsewhere in the brain when naloxone s.c. is used. The localized effect of naloxone may be attributable to its preferential disposition in the lower brainstem area.

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