Influence of anesthesia on bladder hyperactivity induced by middle cerebral artery occlusion in the rat

OSAMU YOKOYAMA,1,2 MITSUHARU YOSHIYAMA,1 MIKIO NAMIKI,2 AND WILLIAM C. DE GROAT1

1Department of Pharmacology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15261; and 2Department of Urology, School of Medicine, Kanazawa University, Kanazawa 920, Japan

Yokoyama, Osamu, Mitsuharu Yoshiyama, Mikio Namiki, and William C. de Groat. Influence of anesthesia on bladder hyperactivity induced by middle cerebral artery occlusion in the rat. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol. 42): R1900–R1907, 1997.—The effect of anesthesia or an N-methyl-D-aspartate (NMDA) glutamatergic antagonist (MK-801) on bladder hyperactivity induced by unilateral middle cerebral artery (MCA) occlusion was examined in female rats. Before infarction, control bladder contractions were monitored in two groups of rats: 1) awake and 2) urethran anesthetized. The awake rats were then anesthetized with halothane, and MCA occlusion was performed in both groups. After recovery from halothane, bladder capacity in awake rats was significantly reduced (60.8 ± 1.3%) 0.5–4.5 h after MCA occlusion but not changed in urethan-anesthetized rats. MK-801 (0.1 mg/kg iv) administered before MCA occlusion blocked the reduction in bladder capacity in awake rats 1.5–4.5 h after MCA occlusion. Bladder capacity was not changed by sham operation in either the awake or urethan-anesthetized rats. Urethan administered after recovery from halothane anesthesia increased bladder capacity in MCA-occluded awake rats but not in sham-operated awake rats. Infarct areas in halothane, urethan-anesthetized, or MK-801-treated rats were not significantly different. These results indicate that cerebral infarction induces bladder hyperactivity in awake rats and that urethan or MK-801 inhibits the development of this hyperactivity, most likely by blocking glutamatergic transmission in the brain.

Damage to neural circuitry in the forebrain can produce hyperactivity of the urinary bladder and urinary incontinence (10, 15, 25). This hyperactivity has been attributed to interruption of inhibitory pathways from the forebrain to a micturition center in the brain stem (i.e., the pontine micturition center, PMC) (24). An experimental model to study the effect of forebrain lesions on voiding function by occluding the middle cerebral artery (MCA) under pentobarbital sodium anesthesia has recently been developed in the rat (12, 13, 29). One day after recovery from the anesthetic, bladder capacity in animals with cerebral infarction was markedly reduced, indicating a hyperactive bladder.

In the present study, we have used the MCA occlusion technique in an attempt to develop an acute model of bladder hyperactivity that can be studied during the first few hours after the infarction. Because pentobarbital sodium produces a prolonged period of anesthesia in the rat and also depresses bladder reflexes, it was necessary to use another anesthetic that was either rapidly reversible (halothane) or long acting (urethan) but with fewer depressant effects on reflex bladder activity. In the course of these studies, we discovered that urethan but not halothane completely blocked the bladder hyperactivity that occurred within 1 h after MCA occlusion.

Although bladder reflexes can be elicited under urethan anesthesia, the effects of drugs on bladder activity, in particular, glutamatergic antagonists, are affected by urethan. For example, it has been shown that the systemic administration of MK-801 (dizocilpine), a noncompetitive N-methyl-D-aspartate (NMDA) glutamatergic receptor antagonist, inhibits the reflex bladder contractions and urethral sphincter activity induced by bladder distension in rats anesthetized with urethan (17, 30, 33). However, in decerebrate, unanesthetized rats, the systemic administration of MK-801 either had no effect or slightly facilitated the contractions of the bladder (31). Similarly, in awake, freely moving rats, the drug increased the amplitude or frequency of bladder contractions (26). Thus the effects of MK-801 on the micturition reflex are markedly changed by urethan.

Urethan also reduces bladder capacity (20, 31), indicating that this anesthetic agent might suppress the tonic inhibitory control of the micturition reflex mediated by forebrain areas (31). Because urethan depresses glutamatergic transmission (7) and influences the effects of glutamatergic antagonists on micturition, it has been proposed that urethan acts in part by suppressing glutamatergic transmission in the neural pathways regulating voiding (31).

Urethan also affects glutamatergic mechanisms in other neural systems. For example, it depresses baroreceptor reflex responses (5), which are thought to be mediated by the release of L-glutamate from the central terminals of baroreceptor afferent fibers (23). Urethan also antagonizes NMDA-evoked depolarization recorded on the ventral roots of isolated spinal cord preparations of the frog or immature rat (6). In addition, even nonanesthetic doses (0.4–0.8 g/kg ip) of urethan are reported to inhibit behaviors induced by the intrathecal injection of NMDA, kainic acid, or quisqualic acid (3).

The depressant effect of urethan on glutamatergic mechanisms and on bladder hyperactivity induced by cerebral infarction raises the possibility that an alteration in glutamatergic transmission may be involved in this bladder dysfunction. Thus further analysis of the actions of urethan on neurogenic voiding disorders.
might lead to a better understanding of the neurotransmitter mechanisms underlying bladder hyperreflexia. In the present study, we evaluated the influence of halothane, urethan, and MK-801, an NMDA glutamatergic receptor antagonist, on the bladder hyperactivity induced by experimental cerebral infarction in rats.

MATERIALS AND METHODS

Thirty-two female Sprague-Dawley rats weighing 250–295 g (mean = 276 g), were used in this study. Rats were divided into six treatment groups (Fig. 1): 1) a control awake group (n = 5) that received no operation except implantation of the cystometry catheter under halothane (2%) anesthesia; 2) an awake sham-operated group (n = 5) that received implantation of the cystometry catheter and sham infarction surgery under halothane anesthesia; 3) an awake cerebral-infarcted group (n = 6) that received implantation of the cystometry catheter and left MCA occlusion under halothane anesthesia; 4) an MK-801 pretreated awake cerebral-infarcted group (n = 6) that received implantation of the cystometry catheter, injection of MK-801 (0.1 mg/kg iv), and left MCA occlusion under halothane anesthesia; 5) a urethan-anesthetized sham-operated group (n = 5) that received implantation of the cystometry catheter and sham infarction surgery under urethan (1.0 mg/kg ip) anesthesia; and 6) a urethan-anesthetized cerebral-infarcted group (n = 5) that received implantation of the cystometry catheter and left MCA occlusion under urethan anesthesia.

Surgical procedure for implantation of the cystometry catheter and MCA occlusion. We adopted the method of Yaksh and co-workers (28) in carrying out cystometry in unanesthetized or urethan-anesthetized rats. Rats were anesthetized with halothane (2%, groups 1–4) or urethan (1.0 g/kg ip, groups 5 and 6), and the bladder was exposed via a midline incision in the abdomen. The bladder end of a polyethylene catheter (PE-60; Clay-Adams, Parsippany, NJ) was heated to create a collar and was passed through a small incision at the apex of the bladder dome, and a suture was tightened around the collar of the catheter. The catheter was tunneled subcutaneously and exited through the skin at the back of the animal. After the abdominal skin was sutured, rats were placed in a restraining cage, and rats in groups 1–5 were allowed to recover from anesthesia. Bladder activity was monitored via the cystometry catheter connected to a pressure transducer. One hour after the implantation of the catheter, control cystometric recordings were performed without anesthesia (groups 1–4) or under urethan anesthesia (groups 5 and 6) by infusing physiological saline at room temperature into the bladder at a rate of 0.04 ml/min.

After control cystometric recording, the rats in groups 2–4 were anesthetized again with halothane (2%). MK-801 (0.1 mg/kg) was given intravenously to rats in group 4 one-half hour before the left MCA occlusion. Occlusion of the left MCA was performed in groups 3 and 4 (halothane anesthetized) and 6 (urethan anesthetized). The left carotid bifurcation was exposed through a midline incision of the neck. After division of the left common carotid artery, the left internal carotid artery was isolated and carefully separated from the adjacent vagus nerve. The left pterygopalatine branch was ligated close to its origin. A 4–0 monofilament nylon thread whose tip had been rounded by exposure to a flame was introduced into the left MCA. The origin of the left MCA was occluded by advancing 17 mm of the thread from the carotid bifurcation (16). The time of the MCA occlusion was ~1.5 h after the implantation of the cystometry catheter (Fig. 1).

In sham-operated animals (groups 2 and 5), the left carotid bifurcation was exposed through a midline incision in the neck, but no further procedures were performed.

Cystometric investigation. All rats were placed in a restraining cage, and rats in groups 2–4 were allowed to recover from halothane anesthesia after surgery. Cystometric examinations were carried out 0.5, 1.5, 2.5, 3.5, and 4.5 h after the sham operation or MCA occlusion in awake (groups 2–4) and anaesthetized (groups 5 and 6) rats.
urethan-anesthetized rats (groups 5 and 6). Saline was infused into the bladder (0.04 ml/min) until the peak of a voiding bladder contraction; the infusion was then stopped, and the saline voided from the urethral meatus was collected and measured to determine the voided volume. By evacuation of the cystometry catheter, residual volume was measured after the micturition reflex. Two cystometric parameters were determined from each cystometry: bladder capacity and bladder contraction pressure. Bladder capacity was defined as the sum of the voided and residual volumes.

The effect of urethan (1.0 g/kg ip) anesthesia on bladder capacity and amplitude of bladder contractions was also examined in awake rats (groups 2 and 3) after completion of the 4.5 h of cystometry recording (Fig. 1). Cystometry was started 1 h after the intraperitoneal injection of urethan.

Techniques for delineating ischemic lesions in the brain. After cystometric investigation, the rat brains (groups 3, 4, and 6) were stained by perfusion techniques with the use of 2% 2,3,5-triphenyltetrazolium chloride (TTC; Sigma, St. Louis, MO) (11). After performing a thoracotomy, we inserted a catheter into the ascending aorta via the left ventricle, perfused it with heparinized saline, and incised the right atrium. After ~1 min, the right atrium was clamped and 50–100 ml of warmed 2% TTC in saline was infused over a period of 4–7 min. After the end of the perfusion, the brain was removed and cut into 2-mm coronal sections. The lesions were quantified by measuring the ischemic area at the coronal section corresponding to optic chiasm.

Data analysis. Data are expressed as means ± SE. Statistical significance was determined by Wilcoxon’s signed-ranks test or Mann-Whitney’s U test. A level of P < 0.05 was considered statistically significant.

RESULTS

Effects of implantation of the cystometry catheter on bladder activity. To study the influence of implantation of the bladder catheter on cystometric parameters, we studied control rats (group 1), which received no operation except the implantation. Bladder capacities 1 and 6 h after the implantation were 0.38 ± 0.05 and 0.42 ± 0.03 ml, respectively (Fig. 2). Bladder contraction pressures 1 and 6 h after the implantation were 30.6 ± 3.7 and 32.4 ± 2.7 cmH₂O, respectively (Fig. 3). The rats in group 1 did not show a significant change in bladder capacity and contraction pressure during the 6 h after the implantation.

Effects of halothane anesthesia on bladder hyperactivity induced by cerebral infarction. In group 2 rats, which received implantation of the cystometry catheter and sham operation under halothane anesthesia, cystometric examinations were performed in the awake state, after the rats recovered from halothane anesthesia. Bladder capacity was not significantly different from that of animals receiving only a bladder catheter (group 1) (Fig. 2). However, in group 3 rats, which received the implantation and left MCA occlusion under halothane anesthesia, bladder capacity was significantly reduced from 0.43 ± 0.06 to 0.16 ± 0.04 ml 0.5 h after MCA occlusion (P < 0.01) and remained consistently <0.18 ml for 4.5 h after MCA occlusion (Figs. 2 and 4). The mean reduction of bladder capacity was 60.8 ± 1.3%. In the awake condition, bladder capacity in cerebral-infarcted rats (group 3) also significantly differed from that in sham-operated rats (group 2).

In awake rats 2.5, 3.5, and 4.5 h after sham operation or MCA occlusion (groups 2 and 3), amplitude of bladder contractions significantly differed from that of control rats (group 1) (P < 0.05, Fig. 3). No significant changes in the amplitude of bladder contractions occurred before or after sham operation or MCA occlusion.

Effects of MK-801 administration before MCA occlusion on bladder activity. In rats of group 4 (pretreated with 0.1 mg/kg MK-801), bladder capacity 0.5 h after MCA occlusion was significantly reduced from 0.49 ± 0.06 to 0.24 ± 0.04 ml (P < 0.01); however, this effect was not detectable 1.5 h after MCA occlusion (Fig. 2). There were significant differences in bladder capacity between group 3 (no pretreatment, MCA occluded) and group 4 (MK-801 pretreated, MCA occluded) rats from 1.5 to 4.5 h after MCA occlusion (P < 0.01–0.05). Six and one-half hours after MCA occlusion, bladder capacity in group 4 rats reached 0.48 ± 0.05 ml, which was the same level as before MCA occlusion. No significant changes in the amplitude of bladder contractions were found before or after MCA occlusion (Fig. 3).

Effects of urethan anesthesia on bladder hyperactivity induced by cerebral infarction. The sham operation in urethan-anesthetized rats (group 5) did not significantly change bladder capacity, although there was a small and gradual increase in capacity at 3.5 and 4.5 h (0.51 ± 0.06 and 0.50 ± 0.04 ml, respectively, vs. 0.40 ± 0.18 ml at 0.5 h after sham operation). In group 6 rats, which received implantation and left MCA occlusion pretreated with MK-801 (0.1 mg/kg iv, n = 6). However, in group 2 rats, which received implantation and left MCA occlusion pretreated with MK-801 (0.1 mg/kg iv, n = 6). Sham operation and occlusion of left MCA were performed under halothane (2%) anesthesia, whereas cystometry was recorded in awake state. Control rats received no operation except implantation of cystometry catheter. Values represent means ± SE. Comparisons between cerebral-infarcted rats and sham-operated rats and between cerebral-infarcted rats with and without MK-801 pretreatment were evaluated by Mann-Whitney’s U test. ∆, Control rats (awake); ○, sham-operated rats (awake); ● (solid line), cerebral-infarcted rats (awake); ● (dotted line), cerebral-infarcted rats (awake, pretreated with 0.1 mg/kg MK-801). *P < 0.05, **P < 0.01 compared with sham-operated rats. †P < 0.05, ††P < 0.01 compared with cerebral-infarcted rats without MK-801 pretreatment.
0.08 ml before the sham surgery) (Fig. 5). In urethan-anesthetized rats, MCA occlusion did not decrease bladder capacity (group 6) but slightly and insignificantly increased capacity from 0.30 ± 0.02 to 0.41 ± 0.03 ml at 0.5–2.5 h after occlusion (Figs. 4 and 5). However, bladder capacities 3.5 and 4.5 h after MCA occlusion were significantly larger (0.46 ± 0.02 and 0.44 ± 0.04 ml, respectively) than the bladder capacity before MCA occlusion (both P < 0.05). After the sham operation or MCA occlusion in urethan-anesthetized rats (groups 5 and 6, respectively), the amplitudes of
bladder contractions gradually decreased during the first few hours and then stabilized (Fig. 3). The changes in amplitude (23.6–28.8% decrease) were statistically significant 2.5–4.5 h after the sham operation (group 5) or MCA occlusion (group 6). There was no significant difference between the cystometric measurements in urethan-anesthetized infarcted and sham-operated rats.

Effects of administering urethan after cerebral infarction. After 4.5 h of cystometric recording, the effects of urethan anesthesia (1.0 g/kg ip) on bladder capacity and amplitude of bladder contractions were examined in awake rats with the sham operation (group 2) or cerebral infarction (group 3) (Figs. 1 and 6). Cystometry was performed 1 h after the intraperitoneal injection of urethan. Before administration of urethan, bladder capacities of groups 2 and 3 were 0.41 ± 0.09 and 0.17 ± 0.03 ml, respectively. Although urethan produced a small, statistically insignificant decrease (14.3%, P = 0.14) in bladder capacity in sham-operated rats, it significantly increased bladder capacity in cerebral-infarcted rats (36.8% increase, P < 0.05). After administration of urethan, the difference in bladder capacity between sham-operated and cerebral-infarcted rats was still statistically significant (P < 0.05).

Urethan did not produce a significant change in amplitude of bladder contractions in either group of animals (Fig. 6B).

Effect of anesthesia or MK-801 on the size of the cerebral infarct. The sizes of the cerebral infarcts induced by MCA occlusion were compared in three groups of animals: group 3, group 4 (pretreated with MK-801), and group 6 (anesthetized with urethan). The mean areas of the infarct, expressed as the percentage of the total area of the brain section, in groups 3, 4, and 6 were not statistically different (22.4 ± 3.9, 23.6 ± 4.5, and 27.6 ± 3.8%, respectively).

DISCUSSION

The present study revealed that a unilateral cerebral infarction induced by occlusion of the MCA in the female rat produces hyperactivity of the urinary bladder. This response occurred when the infarction was induced under halothane anesthesia and was evident as a marked decrease in bladder capacity during slow-infusion cystometrograms performed after recovery from halothane. Pretreatment with MK-801 (0.1 mg/kg iv) 0.5 h before left MCA occlusion blocked the bladder hyperactivity. Similarly, the bladder hyperactivity was also blocked when the infarction and subsequent testing were performed under urethan anesthesia. However, administration of an anesthetic dose of urethan 4.5 h after cerebral infarction when the bladder hyperactivity was well established did not eliminate the hyperactivity. These observations indicate that the short-term effect of brain injury on voiding function is influenced to a considerable degree by the physiological state of the animal at the time of the injury.

In the present experiments, bladder function was evaluated by slow-perfusion cystometry in unanesthetized or urethan-anesthetized rats in which a catheter was implanted in the dome of the bladder. Previous studies of bladder function after chronic implantation of a cystostomy catheter indicated that the bladder is hyperactive during the first few days (20, 28) but returns to normal by day 6 (28). Bladder tissue examined 2 days after implantation exhibited experimental cystitis characterized by severe edema in the submu cosa and an increase in prostaglandin E2 concentration (20). These changes were not observed on days 0 and 7.

A significant decrease in bladder capacity also has been detected 1, 2, and 3 days after implantation in comparison to the capacity on day 0 (20). We therefore used rats immediately after catheter implantation to avoid the influence of experimental cystitis. During the 6-h experiment after implantation of the catheter, bladder capacity was stable, indicating that this acute model should be useful to study the influence of anesthesia, drugs, and neural injury on bladder activity.

It has previously been reported that bladder capacity in rats was significantly decreased as early as 1 day after MCA occlusion (13, 29). This change is presumed to reflect neurogenic bladder hyperactivity. The present
study revealed that the bladder hyperactivity occurs almost immediately, that is, within 1 h after the MCA occlusion. In the former studies, MCA occlusion was performed under pentobarbital sodium anesthesia (40 mg/kg ip); however, in the present studies, it was performed under halothane anesthesia (2%) to decrease the time for recovery from anesthesia. The magnitude of the changes in bladder capacity after recovery from either anesthetic was similar in the two experiments. On the contrary, under urethan anesthesia, bladder capacity after MCA occlusion did not differ from that after a sham operation, indicating that urethan anesthesia alters the influence of cerebral ischemia on bladder reflexes. These findings imply that the type of anesthetic is an important factor in the study of bladder hyperactivity induced by cerebral infarction.

Reflex bladder activity in the neurally intact rat is dependent on an integrative center in the pons that has been referred to as Barrington’s nucleus or the PMC (21, 22). Bilateral lesions of the PMC or transection of the neuraxis caudal to the PMC immediately abolish the micturition reflex. Unilateral cerebral infarction did not eliminate reflex bladder activity, indicating that the functions of PMC were preserved after MCA occlusion. Brain transection experiments in the cat have shown that suprapontine areas of the brain generally exert a tonic inhibitory influence on voiding function (24). Clinical investigations have also suggested that the frontal lobes and the basal ganglia are involved in inhibitory regulation of bladder activity (10, 15). Impairment of this regulatory system after cerebral artery occlusion or hemorrhage is very likely responsible for the development of a hyperactive bladder (25).

Studies of cerebral infarction in rats revealed that bladder capacity correlates with the size of the infarct as determined by TTC staining, i.e., bladder capacity becomes smaller as the area of infarct increases (12). The present studies revealed that size of the infarct did not differ between rats in which the infarction was induced under halothane anesthesia or those in which the infarction was induced under urethan anesthesia. However, rats infarcted under halothane exhibited a 60.8% reduction in bladder capacity after recovery from halothane, whereas the bladder capacity in rats anesthetized with urethan was not decreased after MCA occlusion. These results indicate that urethan anesthesia inhibits the development of bladder hyperactivity that occurs after cerebral infarction.

When urethan was administered after MCA occlusion to unanesthetized rats with small bladder capacities, bladder capacity increased but was still significantly less than the capacity in sham-operated controls. This indicates that urethan anesthesia does not eliminate established neurogenic bladder activity but can block the development of the hyperactivity.

Pretreatment with MK-801 before MCA occlusion also inhibited the sustained bladder hyperactivity in the present study. However, there was a significant decrease in bladder capacity of rats pretreated with MK-801 0.5 h after MCA occlusion. It is likely that this reduction is the result of a suppression of an inhibitory control that is active in the awake animal and dependent on NMDA glutamatergic transmission (26, 31). With the exception of this initial decrease, it is clear that the development of bladder hyperactivity is suppressed when MK-801 is present at the time of the infarction. MK-801 is reported to produce a significant reduction in infarct size, and the reduction is well correlated with the concentration of MK-801 (9). The dose of MK-801 administered in the present study (0.1 mg/kg iv), which is enough to prevent the development of bladder hyperactivity, appears to be too small to reduce the infarct size.

What is the mechanism underlying the action of urethan? In normal rats, urethan can produce various changes in voiding function, including decreases in bladder capacity and contraction amplitude and efficiency of bladder emptying (18, 20, 31, 32). These effects can occur in doses only slightly above the minimal doses required for surgical anesthesia. The dose of 1.0 g/kg ip of urethan used in the present experiments, which is considered to be the lowest dose sufficient to allow surgery without pain (18), elicited a small reduction (14.3% decrease, P = 0.14) in bladder capacity in sham-operated rats. Larger decreases have been reported by other investigators in awake or decerebrate rats (20, 31, 32). This effect of urethan has been attributed to the elimination of an inhibitory control that is tonically active in the awake animal (31). It has been speculated that this effect of urethan might result from blockade of an inhibitory mechanism that is activated by glutamatergic transmission, because the NMDA glutamatergic antagonist MK-801 also decreases bladder capacity in awake rats (as shown in the present study and Refs. 13 and 26), and urethan has been reported to suppress glutamatergic synaptic mechanisms at various sites in the brain (2, 3, 5–8, 14). For example, urethan anesthesia completely blocked partial kindling (2), which involves NMDA-dependent as well as non-NMDA-dependent glutamatergic transmission (8). Urethan also attenuated long-term potentiation (LTP) in the hippocampus, for which NMDA-mediated neurotransmission is crucial (14). On the other hand, synaptic responses mediated by NMDA are relatively insensitive to pentobarbital sodium (19) and halothane (27), two anesthetics that did not block the infarction-induced bladder hyperactivity. The effect of low doses of MK-801 to suppress the bladder hyperactivity after cerebral infarction (13) has also implicated NMDA glutamatergic transmission in triggering the hyperactivity. These data suggest that there are at least two temporally distinct mechanisms that are essential for the bladder hyperactivity induced by cerebral infarction. Both of these mechanisms may depend on NMDA glutamatergic transmission. The first occurs at the time of the infarction and might be considered a triggering mechanism that produces a long-lasting (up to several months) change in the micturition reflex pathway (29). If this mechanism is suppressed by urethan or MK-801 at the time of the
infarction, the abnormal bladder activity does not occur, at least in the initial 6-h postinfarction period.

The second mechanism that appears to depend on NMDA receptors sets the micturition switching circuit to a lower bladder volume threshold (i.e., bladder capacity). This threshold can be reset by administering MK-801 and urethan (13) or partly reset by administering urethan alone (Fig. 4A) after the infarction. It is known that bladder capacity or the set point for the micturition reflex can be altered in a graded manner by injecting inhibitory agents (e.g., γ-aminobutyric acid or enkephalins), antagonists for inhibitory receptors (bicuculline or naloxone), or excitatory agents (glutamate, dopamine) and their antagonists directly into the PMC as well as intracerebroventricularly (4). Thus it is tempting to speculate that cerebral infarction initiates a prolonged enhancement or resetting of the trigger point for micturition by altering one or more of these transmitter systems, i.e., downregulation of a tonic inhibitory pathway or upregulation of an excitatory pathway.

This effect of infarction could be a result of an elimination of neural control by neuronal damage or a direct facilitation of neural mechanisms. If the size of the infarct (measured by the TTC method) reflects accurately the degree of neuronal damage and halothane and urethan produce the same size infarct but only halothane allows the unmasking of bladder hyperactivity, then it seems reasonable to conclude that a prolonged upregulation of synaptic mechanisms rather than elimination of inhibitory input is the most likely explanation for the hyperactivity. This could occur by a mechanism similar to LTP (1). Like the well-known LTP phenomenon in the hippocampus, the initial stage of the long-lasting infarction-induced potentiation of bladder reflexes may depend on glutamatergic transmission, because urethan, which is known to depress NMDA glutamatergic mechanisms (7), as well as MK-801, blocked the bladder hyperactivity. Once the bladder hyperactivity is established, it would appear that it is also dependent on a tonically active NMDA glutamatergic mechanism. This working hypothesis will be evaluated in more detail in future experiments by examining the effects of selective NMDA and non-NMDA glutamatergic antagonists on the two phases of infarction-induced changes in bladder capacity.

In summary, cerebral infarction induced by MCA occlusion appears to occur in two phases: 1) an initiation phase at the time of the occlusion that can be completely blocked by urethan anesthesia or MK-801 but not by halothane or pentobarbital sodium anesthesia and 2) a long-lasting possibly irreversible tonic phase that can be partially antagonized by urethan and completely blocked by an NMDA receptor-blocking agent (MK-801) administered during urethan anesthesia (13). In view of the known actions of urethan on glutamatergic transmission, it is possible that both the initiation and tonic phases of the bladder hyperactivity are dependent on glutamatergic synaptic mechanisms.

Address for reprint requests: O. Yokoyama, Univ. of Pittsburgh, School of Medicine, Dept. of Pharmacology, E1303A Biomedical Science Tower, Pittsburgh, PA 15261.

Received 26 February 1997; accepted in final form 29 August 1997.

REFERENCES


