d-Tubocurarine Accentuates the Burn-induced Upregulation of Nicotinic Acetylcholine Receptors at the Muscle Membrane

C. Kim, Ph.D., M. Hirose, M.D., Ph.D., J. A. J. Martyn, M.D.

Background: Increases in acetylcholine receptors (AChRs) at the muscle membrane, induced by burn injury, have been associated with a hyperkalemic response to succinylcholine and resistance to d-tubocurarine-like drugs. Muscle relaxants often are administered to burn-injured patients in the intensive care unit to facilitate mechanical ventilation. This study in rats tested whether continuous administration of d-tubocurarine in subparalytic doses exaggerates the upregulation of AChRs induced by burn trauma. Subparalytic doses of AChRs were used to avoid the confounding effects of immobilization.

Methods: Three days after an approximate 50% body surface area burn or sham injury, the animals received an infusion of 3.0 ± 0.05 μg/h of d-tubocurarine or equal volume of saline directly to the left gastrocnemius muscle via a catheter connected to a subcutaneously implanted osmotic pump. After 7 days of d-tubocurarine or saline infusion, the AChRs were quantitated using 125I-α-bungarotoxin. The AChRs on the d-tubocurarine or saline-infused left gastrocnemius were compared to the contralateral gastrocnemius in the same group. The right or left gastrocnemius AChRs were compared to the ipsilateral muscles between groups. These intra- and inter-group comparisons allowed the delineation of the effects of catheter irritation, burns, or d-tubocurarine on AChRs.

Results: Daily examination of the withdrawal response to toe-pinch revealed no evidence of paralysis. Weight loss in the burn-injury animals receiving d-tubocurarine or saline was similar, confirming that the infusion of d-tubocurarine did not impair the mobility of the animals to move and feed. The plasma d-tubocurarine concentration after 7 days of infusion was 26.0 ± 12 ng/ml (mean ± SE). Regardless of burn or sham injury or of d-tubocurarine or saline infusion, the concentration of AChRs on the left was consistently greater than in the contralateral right gastrocnemius muscles within the same group, indicating that manipulation of the area alone can result in upregulation of AChRs. The AChRs in the right gastrocnemius of burn-injured animals were greater than those in the same muscle of sham-injured animals, regardless of saline (7.24 ± 0.9 vs. 5.7 ± 0.5 fmol/mg protein, P = 0.06) or d-tubocurarine (7.3 ± 0.4 vs. 5.7 ± 0.5, P < 0.05) infusion to the burn-injury groups. AChRs in the left gastrocnemius of burn-injury animals receiving d-tubocurarine were significantly greater than those in burn- or sham-injury animals receiving saline (13.9 ± 1.1 vs. 9.8 ± 1.2 and 7.1 ± 0.5 fmol/mg protein, respectively, P < 0.05).

Conclusions: Burn-induced upregulation of AChRs is accentuated by infusion of subparalytic doses of d-tubocurarine. Concomitant administration of d-tubocurarine to burn-injured patients may result in further exaggeration of the aberrant responses to neuromuscular relaxants. (Key words: Burns; drug interaction. Neuromuscular relaxants: d-tubocurarine. Receptors: acetylcholine; nicotinic.)

WHEN upregulation (increase) of receptor numbers occurs, it is usually associated with increased sensitivity to agonists and/or resistance (hyposensitivity) to competitive antagonists, whereas downregulation decreases sensitivity to agonists and increases sensitivity to antagonists. Chronic competitive antagonism (inhibition) of a receptor usually results in its upregulation, whereas chronic agonist stimulation results in down-regulation of that receptor. Competitive inhibition of skeletal muscle acetylcholine receptors (AChRs) and the subsequent impaired neuromuscular transmission, produced by continuous infusions of d-tubocurarine, vecuronium, succinylcholine, or α-bungarotoxin has...
been shown to increase AChR numbers, simulating a denervation-like state, despite anatomic continuity between nerve and muscle.\textsuperscript{3,4} Whether the AChR proliferation was due to the drug or some other factor could not be concluded, because the doses used also caused paralysis and/or immobilization of the muscle.\textsuperscript{5-7} Partial or complete immobilization of muscle, in the absence of denervation or competitive antagonists, can upregulate AChRs.\textsuperscript{5-8} Burn injury to skin has been shown to cause an upregulation of AChRs locally and at sites distant from the burn.\textsuperscript{9-15} Although some controversy exists about this,\textsuperscript{14} an increase in AChRs, regardless of etiology, is usually associated with resistance to competitive antagonists, such as d-tubocurarine, metocurine, and atracurium.\textsuperscript{9,15-17} Increased sensitivity to depolarizing relaxants, such as succinylcholine,\textsuperscript{18,19} is a previous study from our laboratory indicated that subparalytic (subtherapeutic) doses of competitive antagonist d-tubocurarine can upregulate AChRs.\textsuperscript{19} Patients with major thermal injury often receive nondepolarizing neuromuscular relaxants for prolonged periods to facilitate mechanical ventilation in the intensive care unit. The current study in rats examines whether the administration of a competitive antagonist in subparalytic doses accentuates the upregulation of AChRs induced by burn trauma; the confounding effects of immobilization thus were eliminated.

Materials and Methods

Burn Injury

All experiments followed and conformed to the animal care guidelines of the Massachusetts General Hospital and Shriners Burns Institute and were reviewed by the Institutional Animal Studies Review Board. These experiments also conformed to the rules and regulations of the National Institutes of Health, which supported these studies. Male Sprague-Dawley rats (Taconic Farms, Germantown, NY; 225–300 g) underwent splenectomy under aseptic conditions during pentobarbital (Abbott, Chicago, IL) anesthesia administered as 50 mg/kg intraperitoneally. Adequacy of anesthesia was tested by the withdrawal response to toe-clamping. Splenectomy, which prevents autotransfusion of blood from spleen, was performed to enhance the shock state of burn injury. Seven days after splenectomy, the animals were reanesthetized with pentobarbital, and a full-thickness third-degree burn injury to the skin was given, as previously described.\textsuperscript{9,20} Briefly, the fur on the trunk was shaved and approximately 50% of total body surface area was injured by immersion in water at 75-85°C. The back and flanks were exposed to the hot water for 10 s each, and the abdomen for 6 s. Control animals were treated the same way as the trauma group but were immersed in lukewarm water. All animals received the same postoperative care. During recovery from anesthesia, all animals were warmed by a heat lamp to maintain body temperature (about 37°C) and were resuscitated with a crystalloid solution 4 mL/kg/\% burn, administered intraperitoneally. After recovery from anesthesia, the animals were allowed crystalloid solution, ad lib, orally. A 1% silver sulfadiazine cream (Silvadine, Marion Labs, Kansas City, MO) was applied to the injured areas. The size of the burn was evaluated on the day of injury (day 1) and at 3 and 10 days after injury. The size of the burn was measured and expressed as a percentage of the total body surface, which was calculated by using the equation 0.0011 × (body weight)\textsuperscript{0.67}.\textsuperscript{21}

Local Administration of d-Tubocurarine or Saline to Left Gastrocnemius

The classic pharmacologic probe of the neuromuscular junction, d-tubocurarine, was used as the test drug. Three days after burn or sham injury, the animals were reanesthetized with incremental doses of intraperitoneal pentobarbital sodium and infusion of d-tubocurarine or saline, initiated via Alzet osmotic pumps (Alza, Palo Alto, CA). These pumps were implanted subcutaneously on the back of the animals, slightly posterior to the scapula. The flow modulator of the pump was connected to PE60 tubing (Becton Dickinson, Parsippany, NJ) and filled with the same solution as that in the pump (d-tubocurarine or saline). The free end of the tubing was threaded subcutaneously from the back to the left leg and placed in close proximity to the insertion of the inner semitendinosus muscle in the popliteal fossa at the upper leg, close to the sciatic nerve. The left gastrocnemius muscle was not touched by the implanted catheter but was exposed to the infused solution. All animals received identical postoperative care. The sham-injury group received saline only. The burn-injury group was subdivided into two groups; one group received saline, and the other received d-tubocurarine. The number of animals in each group is indicated in tables 1 and 2. Because of the potential for a higher mortality in the burn-injury group that received d-tubocurarine, a higher number of animals were studied. The osmotic pump (model 2001) filled with d-tubo-
d-TUBOCURARINE ACCENTUATES UPREGULATION OF AChRs OF BURNS

Table 1. Changes in Body Weight and Size of Burn with Time

<table>
<thead>
<tr>
<th></th>
<th>Sham-Burns with Saline Infusion (n = 10)</th>
<th>Burns with Saline Infusion (n = 9)</th>
<th>Burns with d-Tubocurarine Infusion (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of burn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 days after burn</td>
<td>266 ± 5</td>
<td>270 ± 5</td>
<td>259 ± 6</td>
</tr>
<tr>
<td>10 days after burn</td>
<td>272 ± 6*</td>
<td>247 ± 6*</td>
<td>238 ± 5*†</td>
</tr>
<tr>
<td>Size of burn (% of body surface area)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of burn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 days after burn</td>
<td>308 ± 7*</td>
<td>252 ± 11*</td>
<td>246 ± 5*†</td>
</tr>
<tr>
<td>10 days after burn</td>
<td>—</td>
<td>48 ± 1</td>
<td>47 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43 ± 1†</td>
<td>43 ± 1†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37 ± 1†</td>
<td>35 ± 2‡</td>
</tr>
</tbody>
</table>

* P < 0.001 versus preburn weight in the same group.
† P < 0.001 versus the weight of time-matched sham-burned group.
‡ P < 0.001 versus the size on day of burn.

Curare 2.7 mg/ml (Bristol-Myers Squibb, Princeton, NJ) or an equal volume of saline delivered each of the fluids at a rate of 1.12 ± 0.02 µl/h for 1 week. d-Tubocurarine was administered to burn-injury rats in subparalytic doses; the confounding sequelae of immobilization thus were eliminated. A sham-injury group that received d-tubocurarine was not studied, because previous studies documented that subparalytic doses of d-tubocurarine to normal animals can upregulate AChRs. Furthermore, the intergroup (ipsilateral muscles between) and intragroup (right vs. left within) comparisons in this study allowed the delineation of the effects of catheter irritation versus burns versus d-tubocurarine on upregulation of AChRs.

All animals were checked daily for paralysis of the right and left gastrocnemius muscle by assessing the presence or absence of withdrawal reflex during toe-pinch. Seven days after initiation of d-tubocurarine or saline infusion (10 days after burn or sham injury), the animals were killed by an overdose of pentobarbital. The left gastrocnemius receiving the infusion and the contralateral right gastrocnemius muscles were excised, washed several times in saline, chopped quickly, and frozen in liquid nitrogen. The frozen samples were kept at −70°C until quantitation of AChR number.

Acetylcholine Receptor Assay. The AChR numbers were quantitated by 125I-α-bungarotoxin (125I-α-BTX) (specific activity 16.8 μCi/µg, New England Nuclear, Boston, MA), which binds specifically and irreversibly to the AChRs. The assay procedure was reported previously.10,11 On the day of the assay, the muscles were thawed and homogenized for 1 min in four volumes of 0.1 M potassium phosphate buffer, pH 7.4, containing 1 mM EDTA, 2 mM benzamidine hydrochloride, 0.1 M phenylmethylsulfonyl fluoride, 0.5 mg/ml bacitracin, and 0.02% (w/v) sodium azide at 4°C. The homogenate was centrifuged at 20,000 g for 30 min at 4°C. The precipitates were resuspended and homogenized for 1 min in the same buffer containing an additional 2% (v/v) Triton X-100 (Sigma, St Louis, MO), a detergent that extracts the AChRs. The extraction procedure was continued overnight, on a shaker, in a cold room. The solution was centrifuged at 20,000 g for 50 min at 4°C; the supernatant was recovered

Table 2. AChR Number in the Gastrocnemius Muscles (fmol/mg protein)

<table>
<thead>
<tr>
<th></th>
<th>Sham-Burns with Saline Infusion (n = 10)</th>
<th>Burns with Saline Infusion (n = 9)</th>
<th>Burns with d-Tubocurarine Infusion (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left gastrocnemius</td>
<td>7.13 ± 0.47*</td>
<td>9.84 ± 1.21*</td>
<td>13.93 ± 1.07*‡</td>
</tr>
<tr>
<td>Right gastrocnemius</td>
<td>5.72 ± 0.47</td>
<td>7.18 ± 0.88§</td>
<td>7.33 ± 0.43§</td>
</tr>
</tbody>
</table>

* P < 0.05 left versus right gastrocnemius within each group.
‡ P = 0.06 versus ipsilateral muscle in sham-burned controls.
§ P < 0.05 versus ipsilateral muscle of sham or burned-group receiving saline.
§§ P < 0.05 versus ipsilateral muscle in sham-burned controls.
and stored at −70°C. Triplicate samples of crude muscle extract were incubated with 2.5 nM $^{125}$α-BTX in the 2% Triton buffer for 90 min at room temperature. Excess $^{125}$α-BTX was separated from toxin-bound AChR complex using polyethyleneimine, preextracted Wharton GF/B glass fiber filters by vacuum filtration. Nonspecific binding of $^{125}$α-BTX was detected by preincubation, with excess unlabeled 1 μM of α-BTX. The protein concentration of muscle extract was assayed according to the Hartree method. The number of AChRs was expressed as fmols/mg protein.

**Analysis of Plasma d-Tubocurarine Concentrations.** At the time of killing, blood was extracted into heparinized syringes by cardiac puncture. The plasma was separated and stored at −70°C until the assay. Plasma d-tubocurarine concentrations were analyzed by reversed-phase HPLC method, as described previously. The lower detection limit of the assay was 10 ng/ml of d-tubocurarine in plasma.

**Statistical Analysis.** One-way analysis of variance for repeat measurements and Dunnett’s multiple comparison tests were used to identify the significant differences between groups. The paired t test was used to compare differences within the groups (e.g., AChR changes between right and left gastrocnemius within the same group). A significant difference was assumed if the P value was <0.05. Values were expressed as mean ± SEM.

**Results**

**Body Weight, Size of Burn Injury, and Mobility**

There were no differences in body weights between groups before thermal or sham injury (table 1). No apparent differences in movement or eating behavior were observed after implantation of the pumps. The withdrawal response to pinch, tested daily, was present in all animals. After thermal injury, the sham-injury control group gained weight significantly. The body weights of the experimental groups, however, decreased at 3 days after burn compared to its preburn weight and remained at that weight even at 10 days after burn (table 1). The percentage of body surface area burns did not differ between the burn groups either on the day of the injury or at 3 and 10 days after burn, but there was a decrease in burn size with time (table 1).

**Plasma d-Tubocurarine Concentration**

The plasma concentration of d-tubocurarine in the burn-injury group receiving the drug was 26.0 ± 12.2 ng/ml after 7 days of infusion to the left gastrocnemius. In two animals of the burn-injury group receiving d-tubocurarine, the concentration of d-tubocurarine was less than the detection limits (10 ng/ml) of the assay, and these data were not included.

**AChR Numbers**

Changes in AChR numbers are indicated in table 2. Nonspecific binding of $^{125}$α-BTX was 21.63 ± 0.95%. The left gastrocnemius muscle of all three groups consistently showed significantly greater concentration of AChRs than their contralateral right muscles. The concentrations of AChRs in the right gastrocnemius of the burn-injury group that received saline were increased ($P = 0.06$), compared to the right gastrocnemius in sham-injury animals. The AChR concentrations in the left gastrocnemius of burn-injury animals receiving d-tubocurarine were significantly greater than those in the left gastrocnemius of burn- or sham-injury animals receiving saline. In the burn-injury group that received d-tubocurarine, the right gastrocnemius was exposed to d-tubocurarine because of systemic absorption (20.6 ± 12.2 ng/ml). The AChR concentration in these muscles was greater than that in the same muscle of sham-injury controls but did not differ from the burn-injury group receiving saline.

**Discussion**

The inter- and intragroup comparisons in the three groups have allowed us to distinguish the effects of catheter versus burn versus d-tubocurarine infusion on AChRs. Regardless of burn or sham injury or d-tubocurarine or saline infusion, the AChRs in the left side were always greater than in the contralateral right within the same group. Actual contact with the left gastrocnemius muscles by the infusion catheter was avoided. Therefore, it seems that surgical manipulation of the left side by the implantation of the catheter and the subsequent inflammation will upregulate AChRs. This observation in our study complements the observation by others that degeneration or inflammation of muscle, even the presence of a thread on the surface of an innervated muscle, increases the sensitivity to agonist drugs. The increased sensitivity to agonist is indirect pharmacologic evidence of increased AChRs. The observations of Pavlin et al., whereby AChRs increase after even a 2% burn injury over the gastrocnemius muscle, confirm the role of injury and/or inflammation.
d-TUBOCURARINE ACCENTUATES UPREGULATION OF AChRs OF BURNS

The concentration of AChRs in right gastrocnemius muscle of burn-injury animals, which received an infusion of saline, were greater \( (P = 0.06) \) than that of ipsilateral muscle of sham-injury controls. Power analysis of the data indicated that, if the number of animals in the burn-injury group receiving saline was increased to 20, statistical significance of \( P < 0.05 \) would have been achieved, provided the variability remained the same. AChR concentrations in right gastrocnemius muscle of burn-injury animals receiving infusion of d-tubocurarine (to the left gastrocnemius) were significantly greater than in sham-injury animals. The gastrocnemius muscles in our study were not directly beneath the area of burn injury. Thus, the current study confirms previous observations\(^6\)\(^-\)\(^8\) that burn injury causes the proliferation of AChRs at sites distant from the area of burn. Our findings of increased AChRs after burns contrast with the report of Pavlin et al., who did not find changes in AChRs at sites distant from burn.\(^1\)\(^1\)\(^4\) As stated previously, however, their results documented increases in AChRs at muscle membrane immediately beneath the area of a small burn.\(^1\)\(^5\)

The mature AChR is a pentameric protein with a subunit composition of \( \alpha, \beta, \epsilon, \) and \( \delta \); the immature AChR is composed of \( \alpha, \beta, \gamma, \) and \( \delta \). Thus, in the mature and immature AChRs, mutually exclusive \( \epsilon \) and \( \gamma \) subunits, respectively, are present in addition to other subunits. With motor nerve denervation, the transcripts (mesenger ribonucleic acid levels, mRNAs) of all subunits, including that of \( \gamma \) subunits, increase.\(^6\)\(^6\) The increased AChRs after burn injury probably are not a gene-mediated phenomenon, because the transcripts were increased for only one AChR subunit protein.\(^2\)\(^7\) The absence of detectable levels of \( \gamma \)-subunit mRNAs suggests that the immature form of AChRs probably are not expressed after burn injury and that the upregulation of AChR protein is not related to a nerve-related or denervation-like phenomenon.\(^2\)\(^7\) The absence of a denervation-like state after burns is confirmed by the lack of increases in myogenic regulatory proteins, myo-D and myogenin,\(^2\)\(^7\) which also increase with denervation and decreased muscle activity.\(^2\)\(^8\)\(^-\)\(^2\)\(^9\) Increased assembly and surface expression of AChRs has been shown with increased levels of cyclic adenosine monophosphate in muscle.\(^3\)\(^0\)\(^-\)\(^3\)\(^1\) Burn injury is associated with increased cyclic adenosine monophosphate levels in muscle, the magnitude of which is related to size and location of burn injury.\(^5\)\(^2\)\(^-\)\(^5\)\(^4\) For these reasons, it is tempting to speculate that the increased AChRs after burns probably are related not to a transcriptional phenomenon but to a post-transcriptional mechanism, such as increased assembly and/or cell surface expression of the receptor.

Previous studies by Berg et al.,\(^3\) and Chang et al.,\(^4\) documented in vivo that AChR inhibition by ligands, including muscle relaxants, upregulates AChRs. The doses in these studies, however, caused partial or complete immobilization (paralysis) of muscle. Immobilization alone can induce a proliferation of AChRs in the absence of denervation or inhibition of AChR.\(^6\)\(^-\)\(^8\) The studies of Dodson et al., in which critically ill, intensive-care patients received vecuronium, confirm the upregulation of AChRs by immobilization and/or receptor antagonism.\(^3\) In all of these studies, the confounding effects of immobilization versus drug-induced upregulation of AChRs were not differentiated. We previously confirmed, however, that chronic competitive inhibition of AChRs by d-tubocurarine can upregulate the receptor in unburned rats, even in the absence of paralysis.\(^1\)\(^9\)

In the current study, the d-tubocurarine directly infused to the fossa behind the knee did not cause muscular paralysis of the gastrocnemius muscle. This was tested by daily examination of the mobility of the animals. The absence of paralysis or immobilization was confirmed by daily examination of the withdrawal response to toe-pinch, which was present on both sides in the animals receiving d-tubocurarine. That the weight of the burn-injury animals receiving d-tubocurarine did not differ from the weight of the burn-injury animals receiving saline indicates that the infusion of d-tubocurarine duly impaired the mobility of the animals to feed. The high margin of safety in neuromuscular transmission\(^5\) allowed us to infuse d-tubocurarine with no apparent paralysis. More sensitive measures, such as the response to train-of-four or 50-Hz tetanus,\(^3\)\(^5\) however, may have documented the presence of subclinical paralysis.

The most salient observation in the current study is that concomitant administration of d-tubocurarine to burn-injured animals accentuates the upregulation of AChRs induced by burn injury. The AChRs in the left gastrocnemius of burn-injury animals receiving the direct infusion of d-tubocurarine were higher than those in the same muscles of the other two groups (table 2). The AChRs in the right gastrocnemius of burn-injury animals receiving d-tubocurarine also were significantly greater than that in the ipsilateral side of unburned controls but not higher than in burn-injury animals receiving saline. The fact that the right gastrocnemius AChRs in burn-injury animals receiving d-tubocurarine...
was not higher than that in the same muscle of burn-injury animals receiving saline suggests that the increase of AChRs in the former probably was related to burn and not to the small concentrations of d-tubocurarine. Although the right side was exposed to d-tubocurarine, because of systemic absorption of locally infused d-tubocurarine, the absence of further increases in AChRs, as compared to the right gastrocnemius muscle of the burn-injury animals receiving saline, may be due to inadequate d-tubocurarine levels or insufficient length of exposure. In the previous study, in which upregulation was observed with d-tubocurarine in normal, mobile animals, the mean plasma d-tubocurarine level was 0.4 μg/ml at the end of 2 weeks (vs. 0.26 ng/ml after 1 week in this study). 19 Systemic or local infusions of higher doses were not attempted because of the potential for generalized and localized paralysis. Upregulation of a receptor with small doses of an antagonist is known and has been used to advantage. For example, in congestive heart failure, 36,37 β-adrenoceptors usually are downregulated, and their antagonists are relatively contraindicated because of the dependence of the heart on the remaining adrenoceptors for its inotropy. Despite this contraindication, the use of small doses (indicated by absence of hemodynamic changes) of antagonists upregulated β-adrenoceptors and improved myocardial performance. 36,37 That is, it is not essential to antagonize a receptor to measurable effects (e.g., paralysis) to induce an upregulation. Such a mechanism may have been operative in our studies. Measurement of mRNA levels of AChR subunits and of myoD and myogenin would indicate whether this upregulation by d-tubocurarine is transcriptionally mediated and whether it is related to a denervation-like phenomenon. 27-30 Whether the concomitant administration of muscle relaxants can induce the expression of γ-type or immature AChR protein, similar to that seen after denervation, is important to know and may be relevant to the recent reports of prolonged muscle weakness after chronic use of muscle relaxants. 38,39

In summary, the important findings in the study are that local irritation and, possibly, the related inflammation can upregulate AChRs and that d-tubocurarine can accentuate the burn-induced upregulation of AChRs, even in the absence of immobilization. Burn injury results in aberrant pharmacologic responses, including a lethal hyperkalemic response to succinylcholine and resistance to depolarizing relaxants, both of which are related to quantitative changes in AChRs. 2,18 Neuromuscular relaxants are administered to critically ill burn-injury patients to facilitate mechanical ventilation, decrease oxygen consumption, improve oxygenation, and decrease shivering. 40 Based on the current study, it seems that the administration of even small doses of d-tubocurarine will further upregulate AChRs over and above that seen after burn injury alone. These drug-induced changes of AChRs may result in further exaggeration of the aberrant pharmacologic responses of burn injury.

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d-TUBOCURARINE ACCENTUATES UPREGULATION OF ACHRs OF BURNS

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