Pharmacology Biochemistry and Behavior, Vol. 43, pp. 1065–1070, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Opioid Modulation of Thermal Dehydration-Induced Thirst in Rats

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Received 3 July 1991

BARNEY, C. C., C. M. MORRISON, L. A. RENKAMA AND C. VERGOTH. *Opioid modulation of thermal dehydration-induced thirst in rats.* PHARMACOL BIOCHEM BEHAV 43(4) 1065–1070, 1992.—Male Sprague-Dawley rats were utilized to study the effects of the opioid receptor antagonists, naloxone and naltrexone, on thirst induced by thermal dehydration. In an initial experiment, the depressant effect of naloxone (1.0 mg/kg, IP) on the water intake of rats deprived of water for 24 h was confirmed. In subsequent experiments, rats were thermally dehydrated by exposing them without water to a 40°C environment for 1–4 h. Following heat exposure, rats were injected with either naloxone or naltrexone either IP or ICV. Fifteen minutes later, rats were provided with water and water intake was measured for 2 h. Both naloxone and naltrexone had dose (0.1–5.0 mg/kg, IP)-dependent effects of reducing water intake of rats thermally dehydrated for 3 h. Water intake of rats thermally dehydrated for 2 or 4 h was also attenuated by pretreatment with naloxone. Rats thermally dehydrated for 3 h exhibited decreases in water intake following ICV injection of either naloxone or naltrexone at a dose of 50 μg. Neither naloxone nor naltrexone had an effect on urine output in any experiment. The water intake data support the hypothesis that thirst induced by thermal dehydration in rats is modulated by an opioid mechanism.

Heat Naloxone Naltrexone Opioid Rat Thermal dehydration Water balance Water intake

MANY studies on the physiology and pharmacology of thirst utilize water deprivation of from 12–48 h as a thirst-inducing stimulus. Water deprivation leads to dehydration with a loss of water from both the cellular and extracellular compartments, and loss from either compartment leads to thirst and water intake when water becomes available (1,4,18,32,34). Water deprivation is not the only way animals can become dehydrated. Exposure of homeotherms to hot environments will also lead to dehydration. This thermal dehydration occurs when water lost for evaporative cooling is not replaced. For example, when rats are placed in a hot environment they respond behaviorally by spreading saliva on their bodies to prevent hyperthermia (20). This leads to dehydration and an increase in water intake (2,21,28–30).

In rats, thermal dehydration differs from water deprivation-induced dehydration in several ways. Due to salivary losses, there is a greater loss of electrolytes during thermal dehydration than during water deprivation (30). Core and skin temperatures increase significantly during thermal dehydration (20). Plasma volume decreases less with thermal dehydration than with water deprivation (15,23,27) and the water intake following thermal dehydration has a smaller volemic component than does the water intake following water deprivation (2,28,32). In addition, water deprivation but not thermal dehydration activates the renin–angiotensin system and angiotensin II may play a role in water deprivation-induced thirst but not in thermal dehydration-induced thirst (1,3,26). It is not yet known if thermal dehydration-induced thirst is modulated by the same neurochemicals as water deprivation-induced thirst.

One such group of neurochemicals is the opioid peptides. Studies with opioid receptor antagonists, such as naloxone and the more potent naltrexone, have shown that opioids play a role in stimulating water intake in water-deprived rats (5, 6,9,19,42). The finding that quaternary analogs of naloxone and naltrexone, which do not enter the brain when given peripherally, failed to reduce water intake when given peripherally but did so when given centrally (7,10,25,41) suggests that these agents are working through central opioid receptors to attenuate thirst. This idea is supported by studies in which small doses of opioid receptor antagonists reduce water intake when injected centrally (13,35). In light of the findings that many types of thirsts are modulated by opioid peptides (6,34), heat exposure increases plasma endorphin levels in rats (14), and naloxone and naltrexone increase colonic temperature in heat-exposed rats (22,40), it appeared likely that opioids might be involved in thermal dehydration-induced thirst in this species. This report provides evidence for such an involvement.

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METHOD

Male Sprague-Dawley rats obtained from Harlan-Sprague-Dawley and weighing from 228–520 g were used for these experiments. There were no significant differences in body weights between groups for any individual experiment. Rats were housed singly in hanging stainless steel cages in an animal room. The room was maintained at 24 ± 2°C and illuminated from 7:00 a.m.–7:00 p.m. Except during the experimental periods, rats were allowed water and food (Purina Rat Chow) ad lib. Experiments began between 8:00 and 10:00 a.m. When rats were used for more than one experiment, at least 3 weeks were allowed between successive experiments and no rat was used more than once for the same condition. Thus, a between-subjects design (randomized, independent) was utilized for each experiment. Data are presented as the mean ± SEM. The 95% confidence level was used for all statistical tests. The experimental protocol was approved by the Hope College Animal Care and Use Committee.

The opioid antagonists used were naloxone HCl and naltrexone HCl (Sigma Chemical Co., St. Louis, MO). For the peripheral injections, drugs were dissolved in 0.9% NaCL (saline) solution and administered IP at a volume of 1 ml/kg. Control rats received an equal volume of saline. For ICV injections, saline, naloxone, and naltrexone were injected in a volume of 2 μl. The saline used for injection and for preparation of the naloxone solution was sterile and pyrogen-free and the solutions were filtered through a sterile, pyrogen-free 0.22-μm filter prior to injection. Each rat used for the ICV experiments had a cannula stereotaxically implanted in the left lateral ventricle at least 1 week before the first experiment.

For the cannulation procedure, each rat was anesthetized with a mixture of 100 mg/kg ketamine HCl and 1 mg/kg acepromazine maleate injected IM and 20 mg/kg pentobarbital sodium injected IP. A 10-mm stainless steel 23-ga cannula with a stainless steel stylet was implanted 1.5 mm lateral and 0.4 mm anterior to the bregma and 3 mm below the dura using the atlas of Pellegrino and Cushman (31). The cannula was cemented in place with Cranioplastic (Plastic Products Co., Roanoke, VA), which also covered two stainless steel screws inserted into the calvarium. The stylet was removed and cleaned with 70% ethanol every other day. Injections were made using a 29-ga stainless steel injector that projected 1 mm beyond the end of the cannula and was connected to a 10 μl Hamilton syringe (Hamilton Co., Reno, NV) with PE10 tubing. The syringes and tubing were stored in 70% ethanol prior to use. Injections were made over 30 s and an additional 30 s were allowed before the injector was removed and the stylet replaced. Following the last experiment, rats were deeply anesthetized with pentobarbital sodium and 2 μl Evan's blue dye solution were injected through the cannula. The brain was fixed in situ with 10% formalin, removed, and examined with a dissecting microscope for dye distribution throughout the ventricular system. Data from rats with incorrect cannulae placement were not used.

For both the peripheral and ICV experiments, preweighed water bottles were given to rats 15 min after injections. Water intake and urine output were determined after 0.5, 1, and 2 h by weighing the water and urine containers. In an initial experiment, the effect of naloxone on water intake of rats deprived of water for 24 h was determined. In the remaining experiments, the effects of naloxone and naltrexone on water intake of thermally dehydrated rats were determined. For the water deprivation experiment, 17 rats were weighed and then deprived of water but not food. Twenty-three hours later, rats were reweighed and placed in Nalgene (Rochester, NY) metabolic cages in a walk-in environmental chamber maintained at 25 ± 0.5°C. Forty-five minutes later, eight rats were administered naloxone at a dose of 1.0 mg/kg and nine rats were administered saline. Data were analyzed for statistical significance with Student's *t*-test (16).

At the beginning of each thermal dehydration experiment, food and water were withdrawn and the bladder of each rat was emptied by gentle suprapubic pressure. Each rat was then weighed and placed in a Nalgene metabolic cage. The plastic lid and metal food and water access covers of the cages were replaced with metal screens to facilitate air flow through the cage. The cages were placed in a walk-in environmental chamber maintained at 40 ± 0.5°C for 0–4 h. The cages were then removed from the chamber and rats were reweighed. After injections, rats were then placed in standard Nalgene metabolic cages in an environmental chamber maintained at 25 ± 0.5°C.

The effects of different doses of peripherally administered naloxone and naltrexone on water intake of rats thermally dehydrated for 3 h were determined in two separate experiments. For the naloxone experiment, 10 rats were administered saline and 9 rats were administered naloxone at doses of 0.1, 1.0, and 5.0 mg/kg. The same doses were used for the naltrexone experiment with 15 rats in each group. The data at each measurement period for both experiments were analyzed for statistical significance with a one-way analysis of variance (ANOVA) followed by a posthoc Newman-Keuls test for comparisons between all individual means (16).

Next, the effect of peripherally administered naloxone (1.0 mg/kg) on water intake of rats subjected to different levels of thermal dehydration was determined. Rats were exposed to the hot environment for either 0, 1, 2, or 4 h. For each time period, 12 control and 11 or 12 naloxone-treated rats were used. The data were analyzed for statistical significance with a two-way ANOVA (16) with naloxone treatment and dura-

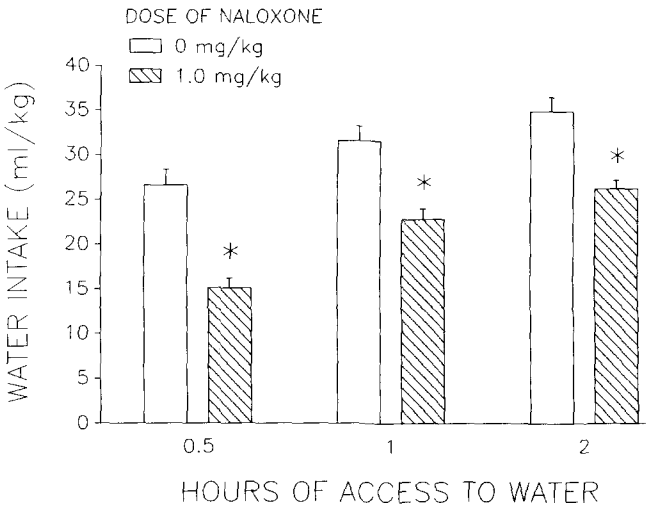

FIG. 1. Mean water intake of rats that had been water deprived for 24 h and administered naloxone at dose of 0 (0.9% NaCl solution) and 1.0 mg/kg IP (n = 9 for the 0-mg/kg dose group and 8 for the 1.0-mg/kg dose group). One SEM is set off at each bar. *Significantly different at $p < 0.005$ from the 0-mg/kg dose value at the same measurement interval.

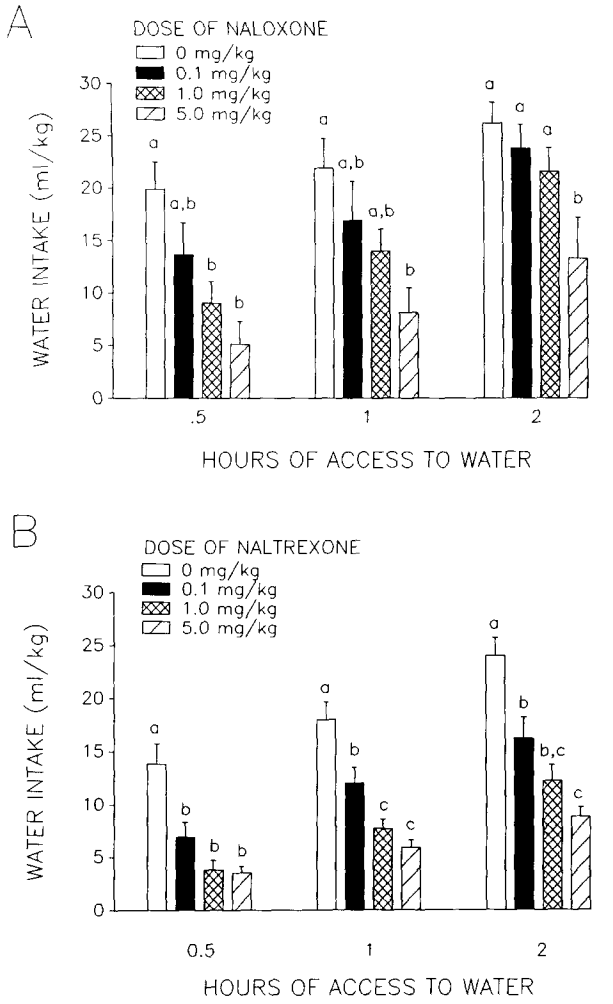

FIG. 2. Mean water intakes of rats dehydrated by exposure to a 40°C environment for 3 h and then administered naloxone (A) or naltrexone (B) at doses of 0, 0.1, 1.0, and 5.0 mg/kg IP. For naloxone, $n = 10$ for the 0-mg/kg dose group and 9 for the other three groups; for naltrexone, $n = 15$ for each group. One SEM is set off at each bar. Mean values not sharing the same letter are significantly different at $p < 0.05$.

tion of heat exposure being the two tested variables. Separate one-way ANOVA tests of the effect of the drug at each time period were also performed.

For ICV experiments, naloxone ($n = 12$ per group) and naltrexone ($n = 7$ per group) were administered at a dose of 50 μg to rats that had been exposed to the heat for 3 h. Data were analyzed for statistical significance with Student's t-test.

RESULTS

Rats deprived of water for 24 h exhibited a robust water intake during 2 h of access to water. Pretreatment with naloxone at a dose of 1.0 mg/kg IP significantly ($p < 0.005$) reduced this water intake (Fig. 1). Exposure of rats to a 40°C environment without water for 3 h also led to a robust water intake when water was made available in a 25°C environment (Figs. 2A and 2B). Administration of naloxone 15 min prior to allowing rats access to water led to a dose-dependent reduction in water intake (Fig. 2A). One-way ANOVA indicated a significant treatment effect at 0.5 h, $F(3, 33) = 6.67$, $p < 0.005$, 1.0 h, $F(3, 33) = 4.25$, $p < 0.05$, and 2.0 h, $F(3, 33) = 4.44$, $p < 0.05$. Individual comparisons indicated that the 5.0-mg/kg dose of naloxone significantly ($p < 0.05$) reduced water intake throughout the 2-h measurement period while the 1.0-mg/kg dose of naloxone significantly reduced water intake during the first 30 min of access to water. At the 1- and 2-h measurement periods, the water intake of rats administered 1.0 mg naloxone/kg was approximately halfway between the water intakes of control rats and rats administered 5.0 mg naloxone/kg.

Naltrexone also had a dose-dependent effect on reducing water intake of rats exposed to heat for 3 h (Fig. 2B). One-way ANOVA indicated a significant effect of naltrexone on the 0.5-h $F(3, 56) = 13.22$, $p < 0.0001$, 1-h, $F(3, 56) = 17.74$, $p < 0.0001$, and 2-h, $F(3, 56) = 17.36$, $p < 0.0001$, water intakes. Even the lowest dose of naltrexone used (0.1 mg/kg) caused a significant ($p < 0.05$) reduction in water intake. Urine outputs following thermally dehydration were small (average 2h urine output = 1.8 ml/kg) and neither naloxone nor naltrexone had any significant effect on urine output.

Water intake of both control and naloxone-treated rats increased with increases in duration of heat exposure (Fig. 3). Naloxone-treated rats had lower water intakes at each duration of heat exposure. Two-way ANOVA of the 1-h water intake data indicated significant effects of both duration of heat exposure, $F(3, 86) = 63.06$, $p < 0.0001$, and naloxone treatment, $F(1, 86) = 14.83$, $p < 0.0005$, and a significant duration × drug treatment interaction, $F(3, 86) = 2.84$, $p < 0.05$. One-way ANOVA at each duration of heat exposure to test for main effects of naloxone showed no significant effects at 0 h, $F(1, 21) = 0.26$, $p > 0.60$, or at 1 h, $F(1, 22) = 1.24$, $p > 0.25$, and significant effects at 2 h, $F(1, 22) = 10.30$, $p < 0.005$, and 4 h, $F(1, 21) = 5.79$, $p < 0.03$. The 0.5-h and 2-h water intake data (not shown) showed similar

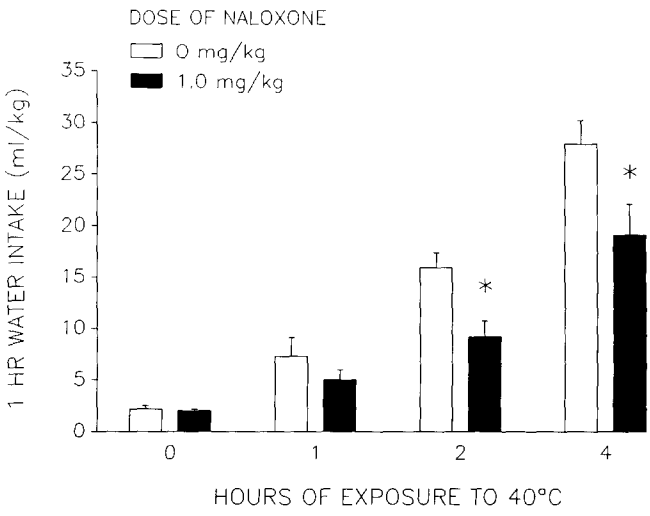

FIG. 3. Mean 1-h water intake of rats dehydrated by exposure to a 40°C environment for 0, 1, 2, or 4 h and then administered naloxone at doses of 0 and 1.0 mg/kg IP ($n = 11$ for the 1.0-mg/kg dose of the 0- and 4-h exposure groups and 12 for all other groups). One SEM is set off at each bar. *Significantly different at $p < 0.05$ from the control group at the same duration of heat exposure.

results except interactions between duration of heat exposure and dose of naloxone were not significant.

Figure 4A shows that naloxone administered intracerebroventricularly at a dose of 50 μg significantly ($p < 0.05$) reduced water intake of thermally dehydrated rats at each measurement period. Naltrexone administered by the same route at the same dose significantly ($p < 0.05$) reduced water intake during the first hour of access to water (Fig. 4B). Neither ICV naloxone nor ICV naltrexone significantly altered urine output during the water access period (data not shown).

DISCUSSION

Previous studies (5,6,9,19,42) have shown that the opioid receptor antagonists naloxone and naltrexone are effective in reducing water intake in water-deprived rats. We confirmed this finding and have further shown that these opioid receptor antagonists are effective in reducing water intake in rats dehydrated by heat exposure. When administered peripherally, naloxone and naltrexone had dose-dependent effects on reducing water intake of rats exposed without water to a 40°C environment for 3 h. As expected because of its greater potency (6), naltrexone was effective in reducing water intake at lower doses than was naloxone. Naloxone's significant inhibition of water intake was limited to rats that had been exposed to heat for at least 2 h. We have shown previously (2) that exposure to 40°C for less than 2 h does not lead to significant levels of thermal dehydration as determined by changes in plasma osmolality and plasma sodium concentration. The present data show that if significant levels of thermal dehydration are reached an opioid receptor-dependent activation of the drinking response appears to occur. Because urine output was not significantly affected by naloxone or naltrexone, it does not appear that opioid receptors are involved in an important way in the control of urine output in thermally dehydrated rats. At doses similar to those used in the current study, these drugs have been reported to reduce water intake in rats due to exercise (17) and administration of angiotensin II (6,25, 34,36,43), isoproterenol (6,25,43), polyethylene glycol (34), salbutamol (42), and hypertonic NaCl solution (12,34,42). With the addition of thermal dehydration-induced thirst to the list with this study, the only type of thirst in rats that the opioid antagonists do not appear to affect is schedule-induced thirst (6,9,42).

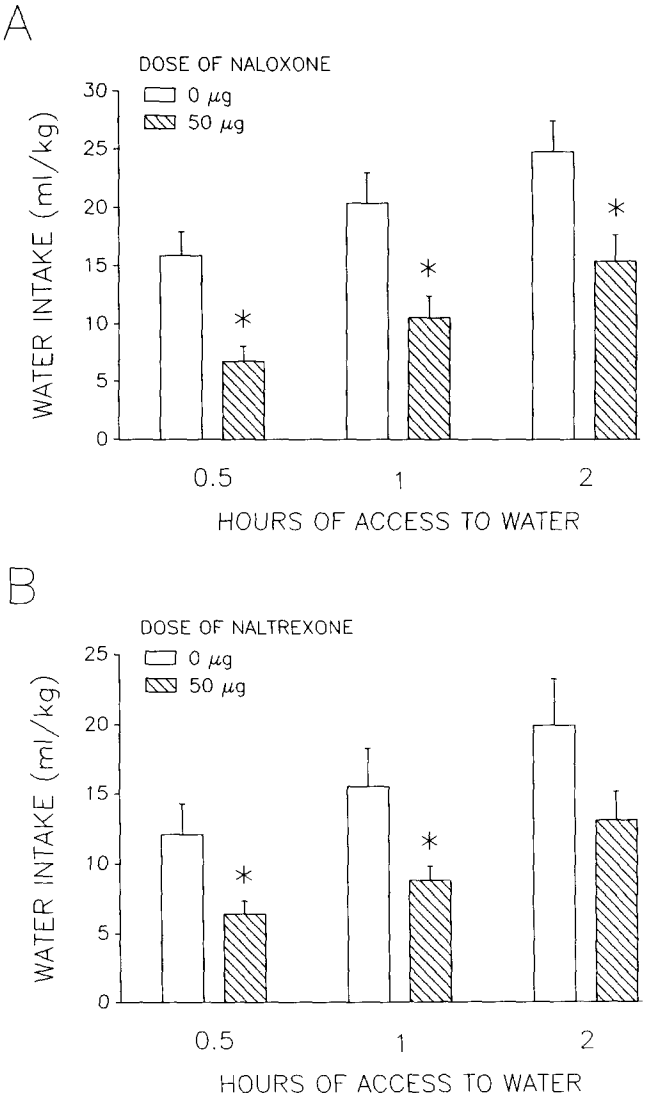

FIG. 4. Mean water intakes of rats dehydrated by exposure to a 40°C environment for 3 h and then administered naloxone (A) or naltrexone (B) intracerebroventricularly at doses of 0 and 50 μg ($n = 12$ for each group for the naloxone experiment and $n = 7$ for each group for the naltrexone experiment). One SEM is set off at each bar. *Significantly different from the control value at the same measurement interval.

ICV administration of either naloxone or naltrexone at the fairly high dose of 50 μg significantly reduced water intake of thermally dehydrated rats. ICV administration of naloxone at doses of 40 or 80 μg reduced water intake due to ICV angiotensin II (8). Sivy et al. (35) reported that bilateral ICV administration of 50 μg naloxone reduced water intake in water-deprived rats but others (13,24) reported that ICV administration of naloxone (12.5-50μg) did not alter water intake in water-deprived rats. Although ICV administrations of opioid receptor antagonists have had mixed results on water intake, the preponderance of evidence does indicate a central site of action of these agents in reducing thirst. Doses of antagonists that had no effect on water intake when administered peripherally did reduce water intake in water-deprived rats when administered into brain tissue at a variety of sites (13,35). Further, quaternary derivatives of naloxone and naltrexone, which do not enter the brain after peripheral administration, have been shown to reduce water intake following central but not peripheral administration (7,10,25,41). It appears likely from our data that the opioid receptors involved in thermal dehydration-induced thirst are also located in the brain.

The precise role of the opioid receptors in the neurochemical pathway of thermal dehydration-induced thirst is yet to be elucidated. Studies of other types of thirsts indicated that there is a complex relationship between activation of opioid receptors and water intake. For example, Summy-Long et al. (37-39) have shown that opioid receptor agonists such as β-endorphin are capable of reducing thirst induced by angiotensin II, polyethylene glycol, and hypertonic NaCl solution. Opioid receptor agonists also reduced water intake in water-deprived rats (11). The reductions in water intake caused by these agonists were reversed by administration of naloxone (8,11,37), which by itself reduces water intake. Because both opioid receptor antagonists and agonists can reduce water intake under a variety of circumstances, there may be two or

more populations of opioid receptors involved in modulating thirst. The mechanism by which opioid receptor agonists modulate thermal dehydration-induced drinking and the exact location of the opioid receptors involved in thermal dehydration-induced drinking remain to be determined. Experiments with more selective opioid receptor antagonists that interact with specific subtypes of opioid receptors may be useful in this regard. However, the data presented in this report and the previous studies showing an activation of the opioid system during heat stress (14,22,40) in rats together suggest that heat stress in rats increases body opioid levels, which then act to increase water intake.

ACKNOWLEDGEMENTS

The authors acknowledge the skillful technical assistance of Kenneth Meeuwsen and the excellent secretarial work of Beverly Kindig and Diane Wickmann. They also thank Dr. Michael Katovich for valuable advice and a critical review of the manuscript. This work was supported by Grant RO1-36857 from the National Institute of Diabetes and Digestive and Kidney Diseases and Grant 8804082 from the Research Experiences for Undergraduates program of NSF.

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