Thromboxane A2 acts on the brain to mediate hemodynamic, adrenocorticotropin, and cortisol responses

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Cudd, Timothy A. Thromboxane A2 acts on the brain to mediate hemodynamic, adrenocorticotropin, and cortisol responses. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R1353–R1360, 1998.—Conditions that increase the formation of thromboxane A2 (TxA2) also result in activation of hemodynamic and adrenocortical responses. The purpose of this study was to test the hypothesis that TxA2 acts directly on the brain to mediate these responses. Adult sheep were chronically instrumented with vascular and intracerebroventricular catheters. The TxA2 analog U-46619 (0, 100, or 1,000 ng·kg⁻¹·min⁻¹) and artificial cerebrospinal fluid (CSF) were infused intracerebroventricularly for 30 min. Heart rate increased in response to 100 ng·kg⁻¹·min⁻¹ U-46619 infusions. Heart rate did not change over preinfusion values in response to the highest infusion rate, but values were elevated compared with the postinfusion period. Mean arterial pressure, ACTH, cortisol, hematocrit, and arterial pH (pHₐ) increased, and arterial partial CO₂ pressure (Paco₂) fell in response to 1,000 ng·kg⁻¹·min⁻¹ infusions of U-46619. Plasma vasopressin concentrations and arterial partial O₂ pressure did not change. In a second study, U-46619 or artificial CSF was infused intracerebroventricularly during prostaglandin synthase blockade. Blockade reduced but did not prevent blood pressure responses to U-46619 infusion, suggesting that the U-46619 infusions increased prostaglandin synthase metabolism to contribute de novo TxA2 or a second metabolite to augment the blood pressure response. Heart rate, pHₐ, Paco₂, ACTH, and cortisol responses to U-46619 were not different with blockade. We conclude that TxA2 acts on the brain to mediate blood pressure, heart rate, pHₐ, Paco₂, hematocrit, ACTH, and cortisol responses. These findings support the hypothesis that TxA2 acts directly on the brain to promote cardiovascular and hormonal responses that may serve a protective function during conditions when TxA2 formation is increased.

METHODS

Adult nonpregnant Rambouillet ewes (n = 6) were anesthetized with halothane, and aseptic surgery was performed. Catheters (polyvinyl chloride, 0.050 in. ID, 0.090 in. OD) were advanced from the femoral arteries and veins into the abdominal aorta and vena cava, respectively. The vascular catheters were then tunneled subcutaneously to the flank region and brought through the skin. A cloth pouch was attached to the skin to contain the catheters. A curvilinear skin incision was made to expose the skull, and a 3-mm hole was bored through the skull 1 cm rostral to bregma and 1 cm lateral to midline. A predrilled plastic plate (2 in. × 1 in. × ½ in., Vivak; US Plastics, Lima, OH) was fixed to the skull over the hole using stainless steel screws (½ in.). An 18-gauge, 2-in. Teflon catheter (Angiocath; Becton Dickinson, Sandy, UT) was passed into the lateral ventricle. The hub of the catheter was removed, and a polyvinyl chloride catheter (0.050 in. ID, 0.090 in. OD) was fixed to the catheter, and the catheter assembly was fixed to the plastic plate using cyanoacrylate

vasopressin; blood pressure; heart rate; prostaglandins; adrenocorticotropic hormone

THROMBOXANE A2 (TxA2), a labile product of prostaglandin synthase metabolism, is produced in many tissues, including platelets, vascular smooth muscle, lung, leukocytes, heart, and brain (21, 22, 34). Synthesis of TxA2 increases during conditions that include endotoxemia, anaphylaxis, circulatory shock, myocardial ischemia, atherosclerosis, coronary vasospasm, and cerebral ischemia (5, 18, 20, 23, 24, 38). TxB₂, the relatively stable metabolite of TxA2 and a useful index of TxA2 formation, is normally present in plasma in low concentrations (<50 pg/ml) but may rise into the nanogram-per-milliliter range during these conditions (24). The homeostatic responses to these conditions include the activation of hemodynamic and adrenocortical responses, leading us to hypothesize that these responses may in part be triggered by TxA2. Low rates of intravenous endotoxin infusion into adult sheep result in the elevation of heart rate, blood pressure, cardiac index, plasma ACTH, and TxB₂ concentrations (8, 18, 38). The blood pressure, heart rate, and hypothalamic-pituitary-adrenal responses to small endotoxin infusions cannot be explained by the modest changes in blood gases secondary to TxA2-induced pulmonary vasoconstriction (29). In addition, the cardiopulmonary responses to endotoxin are prevented by infusions of the TxA₂ receptor antagonist SQ-29548 (18). And, finally, increased formation of TxA₂ in response to peripheral infusions of mineral acid results in elevations of heart rate and hypothalamic-pituitary-adrenal axis activation (12). Together, these findings suggest that responses to endotoxin are at least in part mediated by TxA₂. Although excessive and generalized formation of TxA₂ sufficient to result in widespread platelet aggregation and significant vasoconstriction of pulmonary and peripheral vascular beds likely has a negative impact on survival and recovery, a discrete production of TxA₂, perhaps in the brain, may perform a protective function by stimulating hemodynamic and adrenocortical responses that would act to preserve tissue perfusion. In this study, we have begun to test this hypothesis by infusing the TxA₂ analog U-46619 directly into the central nervous system in conscious, chronically instrumented sheep. A second series of experiments was performed using lateral ventricle infusions of U-46619 during prostaglandin synthase blockade to determine whether responses to the infusion of U-46619 are altered by de novo formation of TxA₂ or a second prostaglandin synthase metabolite other than TxA₂.
glue. Catheters were directed subcutaneously and brought through the skin in the cervical region cranial to the shoulder and a pouch was secured to the skin to protect the catheters. Correct positioning of the lateral cerebral ventricle catheters was determined postmortem by injecting India ink and verifying the location of the ink in the lateral cerebral ventricle after removal of the brain. Animals were treated postoperatively twice daily for 5 days with 25 mg/kg ampicillin trihydrate subcutaneously (Polyflex; Aveco, Fort Dodge, IA) and 2 mg/kg gentamicin sulfate intramuscularly (Gentavet 100; Velco, St. Louis, MO). Animals recovered for 5 days after surgery before experiments were begun. During the surgery recovery period, the animals were habituated to the laboratory on at least 3 different days.

On the day of an experiment, sheep were placed in individual pens. Sheep were studied in pairs to permit them to maintain visual contact with conspecifics so as to avoid anxiety related to separation from herdmates. Studies were designed to allow at least 48 h between experiments. Experiments consisted of a 30-min preinfusion period (−30−0 min), a 30-min infusion period, and a 30-min postinfusion period. During the infusion period, sheep received 9,11-dideoxy-9α,11α-epoxy-methanoprostaglandin F2α (compound U-46619; Cayman Chemical, Ann Arbor, MI) at rates of 0, 100, or 1,000 ng·kg⁻¹·min⁻¹ in artificial cerebrospinal fluid (CSF). Artificial CSF consisted of 152 meq/l Na⁺, 3 meq/l K⁺, 1.6 meq/l Mg²⁺, 25 meq/l HCO₃⁻, 0.5 meq/l PO₄³⁻, and 135 meq/l Cl⁻. Final pH was adjusted to 7.4 using HCl. The volume infusion rate was 0.5 ml/min. All solutions were infused through a 0.22-µm bacteriostatic filter. Each subject received all three treatments to result in a completely repeated-measures design. The treatment order was randomized.

Phasic arterial blood pressure was measured continuously during the 90-min experiments by connecting an aortic catheter to a strain gauge pressure transducer (Isotec; Quest Medical, Allen, TX). The analog voltage output from the transducer was sampled at a rate of 20 Hz using an analog-to-digital converter (DAS 1402; Keithley Metrabyte, Tauton, MA) and a microcomputer. One-minute mean arterial pressure and heart rate values were calculated offline from the digital recordings (Viewdac, Keithley Metrabyte). Blood (6 ml) was obtained twice into chilled polypropylene tuberculin syringes containing 300 µl of 0.5 M EDTA from the second aortic catheter at the beginning of the control period, at the beginning of the infusion period, and then every 10 min until the end of the postinfusion period. Tubes were kept on ice until the end of the experiment, then centrifuged for 20 min at 2,800 g at 4°C. Plasma was separated and stored in separate aliquots at −20°C. Blood (0.5 ml) for blood gas and pH measurements was collected anaerobically in heparinized 3-ml syringes. Blood gases and pH were measured using a blood gas analyzer (model 330; Radiometer, Westlake, OH). Blood for hematocrit measurements was collected into heparinized microhemocrit tubes.

A second series of experiments was performed using the same subjects. The prostaglandin synthase inhibitor indomethacin (10 mg/kg; Sigma, St. Louis, MO) was infused intravenously over 10 min. At 30 min after the beginning of indomethacin infusion, artificial CSF or artificial CSF plus 1,000 ng·kg⁻¹·min⁻¹ was infused into the lateral ventricle over 30 min. Phasic arterial pressure was collected continuously over the 30-min infusion and postinfusion periods. Blood samples were collected at the beginning of the infusion period and every 10 min for 1 h.

Plasma ACTH was measured by commercial radioimmunoassay (Incstar, Stillwater, MN). Validation of this assay for use on sheep plasma has previously been described (9). Cortisol was measured using [1,2,6,7-³H]cortisol (Amersham, Arlington Heights, IL) and rabbit anti-cortisol antiserum kindly provided by Dr. Charles E. Wood, University of Florida. This assay has been completely described elsewhere (40). Before assay, cortisol was extracted from plasma using 20 vol of ethanol. Arginine vasopressin (AVP) concentrations were measured using anti-AVP antiserum, kindly provided by Dr. Wood, and ¹²⁵I-labeled AVP (Amersham). Before assay, AVP was extracted from plasma on bentonite. This assay has been completely described elsewhere (28).

Data are presented as means ± SE. For the first study, treatment (artificial CSF, 100 ng·kg⁻¹·min⁻¹ and 1,000 ng·kg⁻¹·min⁻¹ U-46619) and time were subjected to repeated-measures two-way ANOVA. For the second study, an a priori decision was made to compare treatment groups from the first study (artificial CSF and 1,000 ng·kg⁻¹·min⁻¹ U-46619) with treatment groups from the second study (indomethacin + artificial CSF and indomethacin + 1,000 ng·kg⁻¹·min⁻¹ U-46619) over time using repeated-measures two-way ANOVA. A posteriori analysis was performed using the Student-Newman-Keuls test. Analyses were performed using SigmaStat software (Jandel Scientific, San Rafael, CA). In all cases, the null hypothesis was rejected when P < 0.05. This study was approved by the Institutional Animal Care and Use Committee of Texas A&M University.

RESULTS

Lateral cerebral ventricle infusions of artificial CSF did not result in significant changes in any of the response variables measured. The high U-46619 infusion rate, 1,000 ng·kg⁻¹·min⁻¹, but not the 100 ng·kg⁻¹·min⁻¹ infusion rate, resulted in significant elevations in mean arterial pressure, increasing from 93 ± 3 mmHg at the beginning of the infusion period to peak at 133 ± 5 mmHg 9 min after the end of the infusion period (Fig. 1). Heart rate was significantly elevated in response to the low U-46619 infusion rate, 100 ng·kg⁻¹·min⁻¹, compared with the control infusion group and compared with the control period, increasing from 70 ± 3 beats/min at the beginning of the infusion period to peak at 86 ± 10 beats/min 8 min after the end of the infusion period. Heart rate did not increase in response to the high rate of U-46619 infusion but declined significantly following the end of the infusion period compared with the other treatment groups and compared with the control period in response to the high U-46619 infusion rate; the lowest value was 55 ± 6 beats/min at 27 min postinfusion compared with 69 ± 6 beats/min at the beginning of the infusion period and the peak value of 76 ± 12 beats/min at 17 min of infusion. The largest decrease in heart rate coincided with the peak elevation of mean arterial pressure occurring early in the postinfusion period.

The high U-46619 infusion rate, 1,000 ng·kg⁻¹·min⁻¹, resulted in changes in arterial blood gases (Fig. 2). Arterial partial CO₂ pressure (Paco₂) was significantly decreased by 20 min of infusion compared with the control period in response to the highest U-46619 infusion rate and remained significantly lower than control levels through the end of the experimental period. Arterial pH (pHa) increased significantly in
response to the high U-46619 infusion rate. Values were significantly greater than the control period from 20 min of infusion through the end of the experimental period. The increase in pHa corresponded temporally with the decrease in PaCO2. Arterial partial O2 pressure (PaO2) (Table 1) did not change significantly.

Infusions of U-46619, 1,000 ng·kg⁻¹·min⁻¹, resulted in hypothalamic-pituitary-adrenal axis activation (Fig. 3). Plasma ACTH concentrations increased significantly compared with the other treatment groups and compared with the control period beginning 10 min after the end of the infusion period and remained elevated through the end of the experimental period. Plasma cortisol concentrations increased in concert with the ACTH responses, evidencing a significant elevation by 20 min postinfusion compared with the control period and compared with other treatment groups. Plasma AVP concentrations (Table 1) did not change significantly.

The high infusion rate of U-46619, 1,000 ng·kg⁻¹·min⁻¹, resulted in significant increases in hematocrit (Fig. 4). Hematocrit was significantly increased compared with the control period and the other treatment groups at 40 and 50 min after the beginning of the infusion period, 10 and 20 min, respectively, after the end of the infusion period.

In a second series of experiments, subjects were infused with indomethacin before infusions of artificial CSF or U-46619 (1,000 ng·kg⁻¹·min⁻¹) into the lateral cerebral ventricle were begun. Mean arterial pressure increased significantly over time and compared with indomethacin + artificial CSF in response to indomethacin + U-46619 (Fig. 5). However, the response to U-46619 was significantly reduced by prostaglandin synthase blockade, with a peak value of 133.2 ± 4.7 mmHg without blockade (Fig. 1) compared with 113.4 ± 3.8 mmHg with blockade. Heart rate did not change during the U-46619 infusions following indomethacin but decreased significantly following the end of U-46619 infusion, and responses were not different compared with the group receiving 1,000 ng·kg⁻¹·min⁻¹ U-46619 without indomethacin.

pHa increased significantly compared with the control period in response to U-46619 + indomethacin (Fig. 6). This response was not different compared with the response to the same dose of U-46619 without indomethacin. PaCO2 was significantly decreased compared with the control period in response to U-46619 following indomethacin, and responses were not different from the group receiving the same dose of U-46619 without indomethacin.

Plasma ACTH concentrations did not change in response to indomethacin + artificial CSF but increased significantly over time and compared with indomethacin + artificial CSF in response to indomethacin + U-46619 (Fig. 7). ACTH responses to indomethacin + U-46619 were not different compared with the 1,000 ng·kg⁻¹·min⁻¹ U-46619 treatment group (Fig. 3). Plasma cortisol concentrations increased significantly over time and compared with indomethacin + artificial CSF in response to indomethacin + U-46619. Cortisol responses were not different when comparing between groups receiving 1,000 ng·kg⁻¹·min⁻¹ U-46619 with or without indomethacin.

Hematocrit increased significantly compared with the control period in response to indomethacin + U-46619 but did not change significantly in response to
indomethacin (Fig. 4). AVP and PaO\textsubscript{2} (Table 1) did not change significantly in response to indomethacin or indomethacin + CSF (Fig. 8). Hematocrit responses were not different when comparing between groups receiving U-46619, 1,000 ng·kg\textsuperscript{-1}·min\textsuperscript{-1}, with or without indomethacin (Fig. 4). AVP and PaO\textsubscript{2} (Table 1) did not change significantly in response to indomethacin or indomethacin + U-46619. Mean preinfusion values were 1.0 ± 0.2 pg·ml\textsuperscript{-1} and 101.2 ± 4.8 mmHg, respectively.

**DISCUSSION**

The infusion of the TxA\textsubscript{2} analog U-46619 into the lateral cerebral ventricle resulted in a significant elevation in blood pressure. Eicosanoids formed in the brain move from the extracellular space into the CSF, where they are avidly taken up from the CSF by facilitated transport processes located in the choroid plexus (3, 17). It is likely that U-46619 was subject to removal from the ventricular system to the vascular space by the same mechanisms that perform this function on endogenously produced eicosanoids. Therefore, at least a component of the increase in blood pressure was probably in response to direct peripheral vasoconstriction mediated by U-46619. However, a component of the increase in blood pressure was mediated by a direct action of TxA\textsubscript{2} on the brain. Evidence supporting this conclusion is that the magnitude of the increase in mean arterial pressure was more than threefold higher in response to intracerebroventricular infusions compared with previous experiments in which an equivalent dose of U-46619 was administered intravenously to chronically instrumented sheep; mean arterial pressure increased from 93 ± 3 to 133 ± 5 mmHg in response to intracerebroventricular infusions compared with an increase from 83 ± 5 to 95 ± 5 mmHg in response to an equivalent infusion rate of U-46619 administered intravenously (9). The likely mechanism by which centrally acting U-46619 influences mean arterial pressure is an increase in neurally mediated vasomotor tone and not an increase in cardiac output because heart rate was decreased during the period of highest mean arterial pressure.

Infusion of U-46619 into the lateral cerebral ventricle resulted in prompt changes in heart rate. Heart rate was the most sensitive of the dependent variables measured, increasing in response to U-46619 infusions of 100 ng·kg\textsuperscript{-1}·min\textsuperscript{-1}. At this infusion rate, there was

**Table 1. PaO\textsubscript{2} responses to infusions of U-46619**

<table>
<thead>
<tr>
<th>PaO\textsubscript{2}, mmHg</th>
<th>–30 min</th>
<th>0 min</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
<th>40 min</th>
<th>50 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>103.8 ± 3.2</td>
<td>100.8 ± 4.4</td>
<td>100.0 ± 4.2</td>
<td>99.2 ± 3.4</td>
<td>98.4 ± 1.4</td>
<td>102.9 ± 1.4</td>
<td>95.0 ± 3.0</td>
<td>97.4 ± 2.9</td>
</tr>
<tr>
<td>100</td>
<td>104.3 ± 2.6</td>
<td>100.5 ± 3.9</td>
<td>105.0 ± 2.3</td>
<td>100.4 ± 2.9</td>
<td>101.6 ± 0.9</td>
<td>101.9 ± 3.1</td>
<td>94.8 ± 3.1</td>
<td>96.1 ± 2.0</td>
</tr>
<tr>
<td>1,000</td>
<td>99.6 ± 3.1</td>
<td>99.7 ± 1.3</td>
<td>100.0 ± 2.2</td>
<td>102.3 ± 1.7</td>
<td>101.6 ± 4.1</td>
<td>102.2 ± 3.2</td>
<td>96.8 ± 3.4</td>
<td>101.6 ± 3.0</td>
</tr>
</tbody>
</table>

Mean ± SE values for PaO\textsubscript{2} and arginine vasopressin (AVP) in response to 0, 100 or 1,000 ng·kg\textsuperscript{-1}·min\textsuperscript{-1} infusions of U-46619 at beginning of the control period (–30 min), during the infusion period (0–30 min), and during the postinfusion period (30–60 min). No significant changes were detected.
no detectable increase in blood pressure. The increase in heart rate was in response to U-46619 acting on the brain. Evidence supporting this conclusion is that equivalent or greater rates of peripheral infusion of U-46619 result in far smaller increases in heart rate (9). In addition, the heart rate response began promptly after the beginning of the infusions, likely too soon after the beginning of the infusion period for significant amounts of the U-46619 to have left the central nervous system. At the 1,000 ng·kg\(^{-1}\)·min\(^{-1}\) infusion rate, a dose that resulted in large increases in blood pressure, there was no significant change in heart rate during the infusion period. This was followed by a statistically significant fall in heart rate during the postinfusion period. Although the trend downward in heart rate began near the end of the infusion period, the fall did not achieve statistical significance until after the end of the infusion period. The maximum fall in heart rate occurred together with the maximum increase in mean arterial pressure. The absence of a fall in heart rate during the period of infusion in the group receiving the high infusion rate, when blood pressure was greatly elevated, suggests that U-46619 presented a stimulatory action that offset the expected blood pressure-mediated baroreceptor inhibition of heart rate. On the basis of these observations, we conclude that TxA2 acts on the brain to stimulate heart rate.

Others have investigated the hemodynamic responses to TxA2 infusions into the lateral cerebral ventricle. Siren et al. (35) found that lateral cerebral
ventricle infusions of U-46619 into anesthetized, spontaneously hypertensive rats but not anesthetized, normotensive rats resulted in prompt increases in blood pressure. Heart rate changes were not detected. Our data differ from theirs likely for several reasons. The dose used in their experiments was far higher than ours on a body-weight basis and was delivered as a bolus. As discussed above, the stimulatory actions of TxA2 on heart rate may be suppressed by baroreceptor-mediated reflex heart rate inhibition. It is possible that they may have observed an increase in heart rate had they utilized lower doses of U-46619. Additionally, they used anesthetized rats whereas we used conscious sheep; differences in species and in the state of consciousness also may account for the differences in findings.

Lateral cerebral ventricle infusion of U-46619 resulted in prompt decreases in PaCO2 and concomitant increases in pH. Previously, we reported that peripheral infusions of U-46619 into the carotid artery but not into the vena cava resulted in changes in blood gases like those presented in this study (9). On the basis of these findings, we conclude that the actions of U-46619 on pH and PaCO2 are mediated at the brain. These responses likely were due to changes in respiration because others have demonstrated that increasing de novo production of TxA2 in the peripheral circulation results in an increase in minute ventilation (27, 31). Others have reported that interruption of vagal nerve transmission in anesthetized cats prevents the TxA2-stimulated increases in minute ventilation and concluded that TxA2 acts on pulmonary vagal afferent nerves to mediate the changes in ventilation (32). However, based on our findings, it is also possible that U-46619 infusions act on central respiratory centers and that preventing vagal signal alters a centrally mediated response. Species differences or differences in the state of consciousness also may have been responsible for the differences in responses. Nevertheless, we conclude that TxA2 acts on the brain to alter pH and PaCO2, although it is possible that TxA2 also may act on pulmonary afferent fibers to mediate respiratory responses.

Infusions of U-46619 into the lateral cerebral ventricle resulted in hypothalamic-pituitary-adrenal axis activation. The magnitude of the hypothalamic-pituitary-adrenal axis response was large, resulting in a fourfold increase for ACTH and an 11-fold increase in cortisol concentrations. The finding that both ACTH and cortisol were elevated in response to intracerebroventricular infusions of U-46619 supports the conclusion that TxA2 acts on the brain to activate the hypothalamic-pituitary axis and does not act directly at the adrenal. This interpretation is supported by a report that U-46619 stimulates the release of corticotropin-releasing hormone from explanted rat hypothalamus (2). Further support that the site of action is the brain is provided by previous studies demonstrating that peripheral infusions of U-46619 equivalent to those used in the present study produced far smaller increases in ACTH and cortisol: peak values of 78 ± 38 pg/ml and 32 ± 8 ng/ml in response to intravenous infusions compared with 227 ± 47 pg/ml and 58 ± 36 ng/ml in response to intracerebroventricular infusions for ACTH and cortisol, respectively (9).

The lateral cerebral ventricle infusions of U-46619 in the present study did not result in a change in plasma AVP concentrations. We previously found that peripheral infusions of U-46619 into the carotid artery also failed to increase circulating concentrations of AVP (9). On the basis of these findings, we conclude that TxA2 does not stimulate magnocellular release of AVP. However, these findings do not eliminate the possibility that AVP may be released from parvocellular neurons in response to U-46619 infusion to potentially play a role in mediating the hypothalamic-pituitary-adrenal axis responses.

Blockade of prostaglandin synthase did not alter the heart rate, pHa, PaCO2, hematocrit, ACTH, or cortisol responses to U-46619 infusions. These findings provide further evidence that responses to U-46619 infusions are mediated by PGH2/TxA2 receptor activation and that these responses do not require the formation of a second species of prostaglandin metabolite or de novo formation of TxA2. However, mean arterial pressure responses to U-46619 were smaller after blockade. This finding suggests that U-46619 infusions resulted in the formation of additional TxA2. It is possible that U-46619 gaining access to the peripheral circulation activated platelets to increase de novo TxA2 formation. A second possibility is that U-46619 infusion might result in the formation of a second prostaglandin synthase metabolite in the central nervous system or in the periphery, one other than TxA2, that might influence blood pressure.

TxA2 is one of several eicosanoids that have been demonstrated to act on the brain. Chimoskey and co-workers (4, 14) have reported that PGE2 acts on the brain to mediate increases in heart rate and blood pressure. Although the specific brain site of action was not determined, they found that corticotropin infusions of PGE2 act more potently then intracerebroventricular infusions to mediate heart rate and blood pressure responses. In the sheep, the carotid arteries perfuse all of the brain cranial to the obex (1). Therefore, compounds infused into the carotid arteries would be able to access receptors in all regions of the brain cranial to the obex. On the other hand, intracerebroventricular infusions would only bring agonist in contact with receptors within diffusion distance of the brain ventricular system. Structures a short distance from the ventricular system would be exposed to a relatively higher concentration of the drug than structures at greater distance from the ventricular system. Structures a short distance from the ventricular system would be subjected to lower concentrations. In contrast to PGE2, U-46619 acts more potently to alter heart rate and blood pressure when infused into the lateral cerebral ventricle compared with the carotid infusion site. These findings support the conclusion that PGE2 and TxA2 act at different sites in the brain to stimulate hemodynamic
responses. PGE2 also acts on the brain to mediate hypothalamic-pituitary-adrenal axis responses, as others have reported that microinjections into the preoptic area result in release of ACTH (15) and we have reported that carotid infusions of PGE2 stimulate the hypothalamic-pituitary-adrenal axis (10). In contrast to TxA2, PGE2 acts at the brain to increase magnocellular vasopressin release as intracerebroventricular PGE2 infusions increase plasma vasopressin concentrations (4). These findings demonstrate that, although both TxA2 and PGE2 act on the brain to stimulate hemodynamic and hormonal responses, their respective collection of actions and sites of actions are different, evidence that both TxA2 and PGE2 are neurostimulatory or neuromodulatory substances, each with distinct actions on the brain.

Perspectives

Adrenocorticotropic responses to potent stimuli such as hypotension are very rapid, occurring within minutes of stimulation. Although this study demonstrated that PGH2/TxA2 receptor activation in the brain potently stimulates ACTH, responses to U-46619 were delayed until after the 30-min period of U-46619 infusion. The delayed response is likely due to the confounding effect of elevated blood pressure; whereas ACTH potently and rapidly responds to hypotension, increases in blood pressure as occurred in these experiments in response to U-46619 infusions result in a baroreceptor-mediated tonic inhibitory action on ACTH secretion. Consequently, the ACTH response to U-46619 was only detectable after blood pressure returned to normal following the end of the U-46619 infusion period. This finding provides an example of how control systems responsible for ACTH secretion integrate stimulatory and inhibitory signals.

Eicosanoids are generated within the brain in response to nonspecific stimuli, ischemia, trauma, and seizures and in response to specific chemical mediators and act on discrete regions of the brain to perform a variety of functions (19, 33, 37, 39). TxA2 is a major product of arachidonic acid metabolism in normal brain under basal conditions (6, 13, 25, 26, 30, 36, 39). The putative roles of eicosanoids in the brain include neuro-modulation, temperature regulation, control of hormone release, control of blood pressure and regulation of cerebral blood flow (7, 16, 36). Our findings that PGH2/TxA2 receptor activation at the brain results in blood pressure, heart rate, pH, PaCO2, hematocrit ACTH, and cortisol responses suggest that TxA2 may play a physiological role in activating or modulating these responses. We hypothesize that the physiological role of TxA2 in mediating the responses reported in this study is as a paracrine substance. We estimate that the high infusion rate in the present experiments created U-46619 concentrations in brain tissues in the micromolar range, a concentration that is physiologically achievable in response to local TxA2 formation. The finding that all but one of the response variables failed to respond to the lower infusion rate (that created less than micromolar concentrations within the brain) suggests that TxA2 does not act as an endocrine substance because only local formation of TxA2 would likely produce micromolar concentrations of TxA2 within brain tissue. Increases in local TxA2 formation within the brain would require local stimulation from a circulating signal, a neural signal, or changes in brain perfusion to result in changes in local PaO2 and pH conditions. We speculate that TxA2 formation in the brain increases in response to decreases in brain perfusion to result in physiological responses that serve to promote cardiovascular function and thus cerebral perfusion.

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