The thromboxane A₂ mimetic U-46619 inhibits somatomotor activity via a vagal reflex from the lung

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Pickar, Joel G. The thromboxane A₂ mimetic U-46619 inhibits somatomotor activity via a vagal reflex from the lung. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R706–R712, 1998.—Vagal reflexes from the heart and lungs elicit autonomic as well as somatomotor responses. The purpose of the present investigation was to determine whether the inflammatory mediator thromboxane A₂ inhibits the knee-jerk reflex via a vagally mediated reflex from either the heart or the lung. The thromboxane A₂ mimetic U-46619 (0.8 ± 0.08 µg/kg) was injected through a catheter placed near the right atrium (n = 11), near the aortic arch (n = 7), or into the pericardial sac (n = 4) in 11 chloralose-anesthetized cats. The knee-jerk reflex, elicited by striking the patellar tendon with a solenoid-driven hammer, was used to evaluate somatomotor activity. The mean maximum tension produced by the knee-jerk reflex was 306 ± 21 g (range 154–471 g). Intravenous U-46619 injection inhibited the knee-jerk reflex by 25 ± 6% and increased peak systolic pressure 53 ± 7 mmHg on average. Bilateral cervical vagotomy abolished the somatomotor inhibition but did not reduce the pressor response. Intravenous U-46619 injection inhibited the knee-jerk reflex in two of seven cats and increased peak systolic pressure by 41 ± 11 mmHg. Vagotomy abolished the inhibition in one of the two cats but did not reduce the pressor response. Intrapericardial U-46619 injection did not affect the knee-jerk reflex nor blood pressure. The results indicate that U-46619 inhibited the knee-jerk reflex via a vagal reflex from the lung because the inhibition predominated after intravenous injection and was abolished by vagotomy. Speculation is made that the inflammatory mediator thromboxane A₂ may contribute via a vagal reflex to the depression of motor activity associated with sickness behavior.

viscerosomatic reflex; vagus nerve

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these seven cats intra-arterial U-46619 decreased the amplitude of the knee-jerk reflex by 21 and 22%. Similarly, intravenous U-46619 in these same two cats decreased the amplitude of the knee-jerk reflex by 24 and 31%, respectively. The latency to the onset of inhibition was nearly twice as long after intra-arterial U-46619 injection compared with intravenous U-46619 injection (51.0 vs. 21.0 s and 34.5 vs. 15.0 s, respectively, for each of the 2 cats). Cutting the cervical vagus bilaterally abolished the inhibition induced by intra-arterial U-46619 in one cat (from 21% before to 0% after vagotomy) and reduced the inhibition in the other cat (from 22% before to 14% after vagotomy).

Knee-jerk reflex in response to intrapericardial U-46619. Figure 2C shows the effect of intrapericardial U-46619 injection on the knee-jerk reflex before and
after vagotomy in four cats. Intrapericardial U-46619 did not significantly change the knee-jerk reflex before (0 ± 6%) or after (0 ± 3%) vagotomy. By contrast, intravenous U-46619 decreased the knee-jerk reflex 23 ± 9% in these same four cats, and intra-arterial U-46619 decreased the knee-jerk reflex 22% in one of these four cats.

Blood pressure. Figure 3 contains group data showing peak systolic blood pressure before and after U-46619 injection and before and after vagotomy. Intravenous U-46619 (Fig. 3A) injection significantly increased peak systolic pressure 53 ± 7 mmHg (from 207 ± 13 before to 259 ± 16 mmHg after injection, n = 11). The hypertensive response to U-46619 persisted after vagotomy, with the peak systolic pressure increasing 65 ± 9 mmHg (from 225 ± 20 before to 290 ± 23 mmHg after injection).

Similarly, intra-arterial U-46619 (Fig. 3B) significantly increased peak systolic pressure before and after vagotomy. Before vagotomy, peak systolic pressure increased 41 ± 11 mmHg (from 211 ± 29 before to 251 ± 36 mmHg after injection, n = 7); after vagotomy, peak systolic pressure increased 58 ± 12 mmHg (from 204 ± 32 before to 262 ± 36 mmHg after injection).

In contrast, intrapericardial U-46619 injection (Fig. 3C) did not change peak systolic pressure (from 218 ± 37 before to 223 ± 40 mmHg after injection, n = 4). After vagotomy, peak systolic blood pressure also did not change in response to intrapericardial U-46619 injection (193 ± 55 before and 195 ± 56 mmHg after injection).

DISCUSSION

This study demonstrated that the thromboxane A2 mimetic U-46619 inhibited the knee-jerk reflex. The somatomotor inhibition was a vagal reflex because it was abolished by cutting the cervical vagi. The afferent arm of this vagally mediated viscerosomatic reflex likely arose from sensory nerve endings in the pulmonary region because U-46619 injected near the right atrium significantly inhibited the knee-jerk reflex whereas U-46619 injected onto the surface of the heart did not inhibit the knee-jerk reflex and U-46619 injected into the aortic arch infrequently inhibited the knee-jerk reflex. In the two instances where aortic injection clearly inhibited the knee-jerk reflex, the latency to the onset of attenuation was longer compared with right atrial injection. The longer latency after intra-arterial injection is consistent with recirculation of U-46619 to the lung. Alternatively, the inhibition evoked by intra-arterial U-46619 injection might have been caused by an extravagal mechanism.

Activation of vagal C fibers likely caused the somatomotor inhibition. U-46619 undoubtedly stimulates vagal afferent C fibers (22). However, U-46619 also activates slowly (SAR) and rapidly (RAR) adapting pulmonary receptors, but their discharge frequency is
four times weaker, on average, compared with the C fiber discharge (22). Moreover, SARs and RARs do not contribute to the vagally mediated respiratory reflexes initiated by U-46619, at least in the cat (5, 22). Therefore it seems unlikely, although not proven directly, that vagal afferent fibers other than C fibers caused the inhibition of the knee-jerk reflex in the present study.

The rise in peak systolic blood pressure was not responsible for the somatomotor inhibition because vagotomy abolished the U-46619-induced inhibition of the knee-jerk reflex but did not abolish the pressor response. In fact, peak systolic blood pressures were slightly higher after vagotomy. In the one cat where vagotomy did not abolish the somatomotor inhibition, an extravalvular mechanism may underlie the inhibition. Similarly, vagal and extravalvular mechanisms underlie the inhibition of the knee-jerk reflex produced by intravenous serotonin injection, although the extravalvular pathway remains unknown (13). It is worthwhile noting in this one cat that U-46619 evoked a pressor effect greater than the pressor effect in any of the other 10 cats (Δ84 vs. Δ71 mmHg before vagotomy and Δ109 vs. Δ86 mmHg after vagotomy, respectively). The hypertension or circulation of U-46619 to the carotid sinus may have caused the inhibition reflexly via the ninth cranial nerve because mechanical and chemical stimulation of the carotid sinus nerve can inhibit motor output (8, 17). Alternatively, the inhibition may have been unrelated to the large change in blood pressure but caused by stimulation of group III and IV muscle afferents (23), the discharge of which may inhibit motor output (20).

The pressor response to intra-arterial and intravenous U-46619 suggests that the U-46619-induced vasoconstriction likely predominated in the systemic circulation. Thromboxane A₂ contracts vascular smooth muscle in the systemic and pulmonary circulations (31, 32). U-46619 injected into the abdominal aorta (23) increases arterial blood pressure to a level similar to that measured in the present study after intra-arterial U-46619 injection. Intravenous U-46619 injection consistently increases pressure in the pulmonary circulation, but it can increase, decrease, or have no effect on pressure in the systemic circulation. For example, in the chloralose-urethan-anesthetized cat, right ventricular pressure increases by nearly 100%, but systemic arterial pressure decreases by nearly 20% during very slow (6–8 min duration, ~1.5 µg) intravenous U-46619 infusion (32). Slightly faster (3–4 min duration, ~1.8 µg) U-46619 infusion increases right ventricular pressure only 75% and increases systemic arterial pressure 3–17% in the cat (22). However, in the chloralose-urethan-anesthetized rabbit right ventricular pressure increases by 60% but systemic arterial pressure decreases by 9% during rapid (10 s duration, 0.5 µg/kg) intravenous U-46619 injection (5). In the unanesthetized goat, pulmonary and systemic arterial pressures increase 350 and 30%, respectively, during moderately slow (5 min duration, 2 µg/kg) intravenous U-46619 infusion (4). Carrithers et al. (4, 5) suggest that the relative strength of systemic versus pulmonary vasoconstriction determines the change in systemic arterial blood pressure. Pulmonary vasoconstriction would decrease left ventricular end-diastolic filling, thereby decreasing cardiac output. The relative strength of the systemic vasoconstriction would determine the hypotensive effect. In the present experiments, right ventricular pressures were not measured, but rapid (2 s duration, 0.8 µg/kg) intravenous U-46619 injection increased peak systolic pressure by nearly 25%. It seems reasonable to suggest that the rapid injection of U-46619 provided a short duration over which this vasoconstrictor was present in the pulmonary circulation and thus increased the relative strength of systemic versus pulmonary vasoconstriction. Clearly, the pressor response was not a vagal reflex because the hypertension persisted after vagotomy.

The absence of a depressor response after intrapericardial U-46619 injection suggests that thromboxane A₂ is not an endogenous chemical capable of evoking the coronary chemoreflex. Previous studies demonstrate that intravenous U-46619 evokes a breathing pattern (22, 31, 32) similar to the vagally mediated pulmonary respiratory chemoreflex (9, 10), and many chemicals, including serotonin, phenyl biguanide, and nicotine, that evoke the pulmonary respiratory chemoreflex also evoke the pulmonary depressor chemoreflex and coronary chemoreflex (10, 25, 33, 35). Thus it seemed reasonable to expect that intravenous and intrapericardial U-46619 would evoke a reflex hypotension. However, evidence showing that U-46619 induces the pulmonary depressor chemoreflex and the coronary chemoreflex was not obtained. The absence of a depressor response after intravenous U-46619 in the present study and in previous studies (4, 22) might be due to U-46619's direct vasoconstrictor effect (31, 32) overriding the pulmonary depressor chemoreflex. Although a distinction has been made between the coronary chemoreflex [evoked by chemical injection into the coronary arteries (10)] and the epicardial chemoreflex [evoked by chemical injection into the pericardial sac (33)], the same chemicals often evoke both of these reflexes (10, 25, 33, 35). However, in the rabbit for example, intravascular but not intrapericardial phenyl biguanide injection elicits a depressor reflex from the heart (1). U-46619's lack of effect on cardiac reflexes in the cat could be confirmed by injection into the coronary vessels.

Although intravenous U-46619 inhibited the knee-jerk reflex via a vagal reflex, the latency to the onset of inhibition after injection was surprisingly long. Somatomotor inhibition attributable to sensory receptors in lung typically occurs within 2–7 s and almost always within 14 s after right atrial injections of serotonin, phenyl biguanide, and nicotine (11, 17). In addition, vagal C fibers often discharge within 2.5 s of right atrial phenylbiguanide injection (27). These short onset latencies have been used to argue for the heart and the lungs as the site of the reflex's origin because the circulatory times are sufficiently short that the injection would not have had time to reach other tissues (14). In the present experiments, the average response...
latency after intravenous U-46619 injection was 18 s. Interestingly, this latency is similar to the latency of other vagal responses after intravenous U-46619 injection. For example, vagal C fiber discharge increases 20 s after U-46619 injection (see Figs. 2 and 3 in Ref. 22). In addition, vagally mediated respiratory reflexes occur at least 25 s after U-46619 injection in the cat (see Fig. 3 in Ref. 32). Furthermore, the response of group III and IV muscle afferents to abdominal aortic injection of U-46619 (23) is substantially longer (27 s) than the response to capsaicin (~6 s) or bradykinin (~21 s). These long latencies raise the possibility that U-46619 binding to its receptors (7) may not be the proximate event that depolarizes the receptive endings of vagal C fibers.

Perspectives

Substantial evidence demonstrates that the vagus nerve is involved in adaptive responses during illness. Systemic infection and inflammation produced by the endotoxin lipopolysaccharide (LPS) elicit a variety of sickness behaviors, including decreased motor activity, fever, hyperalgesia, and decreased appetite (19, 24, 38). These physiological and behavioral symptoms likely contribute to these sickness behaviors via their responses by the organism (19). Proinflammatory cytokines contribute to these sickness behaviors via their action on the nervous system (24, 38). In particular, the abdominal vagus nerves signal the presence of these cytokines (2, 37). Sectioning the vagus nerves subdia-phragmatically blocks or decreases the fever, hyperalgesia, and decreased motor activity elicited by interleukin-1 or LPS (2, 36, 37).

The present study provides additional evidence for the role of the vagus nerve during illness. The stable thromboxane A2 analog U-46619 reflexly inhibited the knee-jerk reflex via a vagal reflex from the lung. Systemic infection, produced experimentally by LPS injection, also increases thromboxane A2 (3, 26), and the increased thromboxane A2 activates respiratory reflexes whose afferent arm consists of vagal afferents from the lung (3). Because U-46619 reflexly inhibited central circuits associated with muscle activity in the present study, endogenous thromboxane A2 released during infection or inflammation may contribute reflexly to the reduced motor activity accompanying sickness. It is worthwhile noting within this context that vagal reflexes from the thoracic viscera may contribute to exercise intolerance when demands made on the cardiopulmonary system exceed its capacity to meet them, such as in patients with congestive heart failure (16, 29, 30). Future research is needed to clarify how information contained within sensory feedback from visceral organs contributes to the organism’s motor state.

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