Cyclooxygenase inhibition potentiates the renal vascular response to endothelin-1 in humans

GUNVOR AHLBORG AND JAN M. LUNDBERG
Department of Clinical Physiology, Huddinge University Hospital, S-141 86 Huddinge, Sweden

Ahlborg, Gunvor, and Jan M. Lundberg. Cyclooxygenase inhibition potentiates the renal vascular response to endothelin-1 in humans. J. Appl. Physiol. 85(5): 1661–1666, 1998.—Vascular endothelin-receptor stimulation results in vasoconstriction and concomitant production of the vasodilators prostaglandin I2 and nitric oxide. The vascular effects of cyclooxygenase (COx) blockade (diclofenac intravenously) and the subsequent vasoconstrictor response to endothelin-1 (ET-1) infusion 30 min after diclofenac were studied in healthy men. With COx blockade, cardiac output (7%) and splanchnic (14%) and renal (12%) blood flows fell (all P < 0.01). Splanchnic blood flow returned to basal value within 30 min. Mean arterial blood pressure increased (4%, P < 0.01). Splanchnic glucose output fell (22%, P < 0.01). Subsequent ET-1 infusion caused, compared with previous ET-1 infusion without COx blockade (G. Ahlborg, E. Weitzberg, and J. M. Lundberg, J. Appl. Physiol. 77: 121–126, 1994; E. Weitzberg, G. Ahlborg, and J. M. Lundberg, Clin. Physiol. (Coln.) 13: 653–662, 1993), the same increase in mean arterial blood pressure (4%), decreases in cardiac output (13%) and splanchnic blood flow (38%), but no significant change in splanchnic glucose output. Renal blood flow reduction was potentiated (33 ± 3% vs. 23 ± 2%, P < 0.02), with a total reduction corresponding to 43 ± 3% (P < 0.01 vs. 23 ± 3%). We conclude that COx inhibition induces renal and splanchnic vasoconstriction. The selectively increased renal vascular responsiveness to ET-1 emphasizes the importance of endogenous arachidonic acid metabolites (i.e., prostaglandin I2) in counteracting ET-1-mediated renal vasoconstriction.

diclofenac and endothelin-1 infusion; cardiac output; splanchnic and renal blood flows; arterial levels of endothelin-1; insulin; glucagon and catecholamines; splanchnic glucose output.

THE VASCULAR ENDOTHELIUM takes part in several processes, including vasoconstriction and vasodilatation. A polypeptide, with vasoconstrictor properties named endothelin, later called endothelin-1 (ET-1), was isolated from cultured porcine aortic endothelial cells, sequenced, and cloned in 1988 (29). ET-1 has been shown to be the most potent vasopressor peptide characterized (23), with long-lasting action in rats (29). We have previously shown that intravenous infusion of ET-1 in humans is followed by long-lasting vasoconstriction in the splanchnic and renal circulations (2, 27), as well as reduction in splanchnic glucose output (2, 3). Whereas plasma disappearance curves showed two half-lives of ET-1 of −1.5 and 35 min, the duration of vasoconstriction was 1 h in the splanchnic and 3 h in the renal circulation (27), respectively. These long-lasting effects have been ascribed to the tight binding of ET-1 to its receptors (15). The difference in vascular responses to ET-1 may be explained by different populations of ET receptors.

Two types of ET receptors belonging to the G-protein-coupled superfamily have been cloned, the ETA-type (5), which is expressed in vascular smooth muscle, and the ETB-type, expressed in the endothelium (see Ref. 23). ETA-receptor activation stimulates phospholipase C and formation of inositol trisphosphate, which, in turn, mobilizes intracellular calcium and diacylglycerol, resulting in phosphorylation of contractile proteins and smooth muscle contraction (18, 21). ETB-receptor stimulation is also followed by influx of extracellular calcium (26). Activation of the endothelial ETB receptor results in release of nitric oxide (NO) (12, 17) and prostaglandin I2 (PGI2) (12), which, by acting on smooth muscle, is followed by formation of cGMP, cAMP, reduced intracellular calcium, and vasodilatation. Furthermore, a smooth muscle ET receptor with ETB-like characteristics has been described on human vascular smooth muscle, where it mediates vasoconstriction (10). Thus ET-1 can act via different receptors and different signal transduction pathways to bring about two diametrically opposed effects: vasoconstriction and vasodilatation.

Increased plasma levels of ET-1 have been described for virtually all pathophysiological conditions in the cardiovascular system, e.g., myocardial infarction (19), cardiogenic shock (8), essential hypertension (22), as well as pulmonary hypertension (24). Cyclooxygenase (COx) inhibition increases the pressor response to ET-1 in guinea pigs (12), indicating a moderating effect of prostaglandins on ET-1-induced vasoconstriction. The present study was undertaken to investigate the effect of COx inhibition per se on cardiac output (CO) and splanchnic and renal vasoactivity and to determine whether COx inhibition alters the response of these variables to a subsequent ET-1 infusion in healthy male volunteers.

METHODS

Subjects

Eight healthy male subjects (age 26 ± 1.7 yr; height 183 ± 2.3 cm; weight 76 ± 1.9 kg) were studied in the resting 12- to 14-h postabsorptive basal state and received infusions of both the COx inhibitor diclofenac and ET-1. All subjects were informed of the purpose and possible risks before giving their voluntary consent. Approval was obtained from the Local Ethics Committee. The investigation conforms with the principles outlined in the Declaration of Helsinki (BMJ, 1964, xx: 177).

Procedure

All subjects were studied while they were in the supine position after an overnight fast. All catheters were inserted
punctaneously. One thin Teflon catheter was introduced into an antecubital vein for infusion of dye indicators for determination of blood flow. Another was inserted into the brachial artery for blood sampling and blood pressure measurements.

Teflon catheters were introduced in the femoral vein and advanced to the hepatic vein in all eight subjects and to a renal vein in four of these subjects, under fluoroscopic control. In the other four subjects, a balloon-tipped catheter was introduced into an antecubital vein and advanced to a branch of the pulmonary artery under fluoroscopic control. Pulmonary capillary wedge pressure was monitored by pressure recording and fluoroscopy. Diclofenac (Voltaren, Ciba-Geigy, Basel, Switzerland) dissolved in saline was administered intravenously over a 5-min period at a dose of 75 mg. Pulmonary oxygen uptake was determined and blood samples were drawn simultaneously from the brachial and pulmonary arteries and the hepatic vein in the basal state and at 10, 20, and 30 min after the diclofenac administration for determinations of dye concentrations (in the brachial artery and hepatic vein), oxygen content, and arterial ET-1 levels. Thirty minutes after administration of diclofenac, a 20-min ET-1 (Pensinsula Laboratory, Belmont, CA) infusion was initiated. The infusion rate was 4 pmol·kg⁻¹·min⁻¹. Pulmonary oxygen uptake was determined and blood samples were drawn from all sites at 20 min of ET-1 infusion.

Continuous recording of heart rate (HR) and mean arterial pressure (MAP) was performed in all subjects. Mean pulmonary arterial pressure (MPAP) and mean pulmonary capillary wedge pressure (PCWP) were registered, and CO was estimated according to the Fick principle on the basis of pulmonary oxygen uptake and systemic arterial-pulmonary arterial oxygen difference [(a-pa)O₂] in four subjects. Splanchnic and renal blood flows were determined in all subjects by constant infusions of cardigreen and p-aminohippurate as previously described (1). For calculation of renal blood flow, the fractional extraction of p-aminohippurate (the arterial minus renal venous concentration divided by arterial concentration) was assumed to be 0.9 in those four subjects who were not fitted with a renal vein catheter. In all subjects, arterial insulin, glucagon, and glucose concentrations as well as hepatic vein glucose concentrations were determined before and after diclofenac administration, as well as during and after the ET-1 infusion.

Analyses

Plasma ET-1 concentrations were assessed by the radioimmunoassay technique. Plasma aliquots (1 ml) were extracted with acid ethanol and dried under a nitrogen stream. For determination of ET-1, ET-1 antiserum (E1) and 125I-labeled ET-1 (Amersham) were used. The detection limit for the assay was 0.40 fmol/tube. Expressing the ET-1 value as 100%, the cross-reactivity of the antiserum used is 16% for ET-1 (1—21), 27% for ET-2, 8% for ET-3, and 0.045% for Big ET-1 (1—38). No cross-reactivity with Big ET-1 (22—38) was observed at concentrations up to 1 µM. The intra- and interassay variations were 6 and 14%, respectively (14). For characterization of the immunoreactivity in the extracted samples, extra samples were subjected to reverse-phase HPLC. Oxygen saturation and hemoglobin concentration in blood were determined with an OSM 3 radiometer and blood gases with an ABL 520 radiometer (Radiometer, Copenhagen, Denmark). Oxygen content in expired air was determined with a zirconium oxide cell (oxygen analyzer S-3A/I, Ametek, Pittsburgh, PA) and carbon dioxide content by the infrared technique (Ametek carbon dioxide analyzer CD-3A). The radioimmunological techniques used to analyze insulin and glucagon as well as the glucose dehydrogenase method for glucose measurement have been described previously (1).

Calculations

Systemic vascular resistance (SVR) was calculated as MAP/CO, and pulmonary vascular resistance (PVR) was calculated as (MPAP − PCWP)/CO.

Data are presented as means ± SE. Because of the experimental setup, the postdiclofenac data were treated separately. ANOVA, according to the repeated-measures design, was used for basal, 10-, 20-, and 30-min postdiclofenac data, followed by Fisher’s protected least-significant difference test, i.e., the interpretation of a significant effect by computing Student’s t-test between all means in the effect; “protected” indicates that the test is preceded by a significant F-test. When the variances differed too much, giving F-values not allowing for ANOVA, logarithms were used to achieve homogeneous variances (see Ref. 1). The ET-1 effects (at 20 min of ET-1 infusion) were compared with the 30-min postdiclofenac data by using Student’s paired t-test (see Table 1). For comparisons with previous results with ET-1 infusion, Student’s unpaired t-test was used (see Table 1 and Fig 1).

RESULTS

Effects of Diclofenac Administration

P values are according to Fisher’s protected least-significant difference test after a repeated-measures ANOVA for data in the basal state and up to 30 min postdiclofenac.

HR, pulmonary oxygen uptake, (a-pa)O₂, CO, and splanchnic and renal blood flow and oxygen uptakes (Table 1). HR did not show a consistent change after diclofenac administration. Similarly, pulmonary oxygen uptake remained unchanged. (a-pa)O₂ rose from 45 ± 2 to 49 ± 3 ml/l at 20 min after the administration of diclofenac (P < 0.01) and then fell. CO fell after diclofenac from 5.89 ± 0.32 to 5.45 ± 0.35 l/min at 20 min (P < 0.01), followed by an increase (P < 0.01) back to basal value 30 min after the administration. Splanchnic and renal blood flow dropped by an average 14 and 12%, respectively, at 10 min after diclofenac (P < 0.001). Splanchnic blood flow increased (P < 0.05) toward basal level 30 min after diclofenac, whereas the suppression of renal blood flow was unchanged and 15% below basal value at that time (P < 0.001). The splanchnic and renal oxygen extractions changed in parallel with the blood flow changes, and consequently the splanchnic and renal oxygen uptakes remained unchanged after diclofenac.

Systemic and pulmonary blood pressure and vascular resistance (Table 1). MAP increased from the basal value of 92 ± 2 to 96 ± 3 mmHg at 10 min after diclofenac (P < 0.01), was still elevated at 20 min (P < 0.05), but did not differ from basal value 30 min after diclofenac. SVR changes did not, because of the few observations (4 subjects), attain statistical significance (repeated-measures ANOVA, P < 0.1). MAP, PCWP, and PVR were unchanged after diclofenac. Splanchnic (VRspl) and renal (VRV) vascular resistance increased within 10 min after diclofenac (P < 0.001). Although RVR was unchanged at 30 min after diclofenac, VRV
Table 1. HR, pulmonary $\dot{V}O_2$, (a-pa)$_O_2$, CO, BF$_{Spl}$, RBF, $\dot{O}_2$$_{Spl}$, $\dot{O}_2$renal, MAP, MPAP, PCWP, SVR, PVR, VR$_{Spl}$, RVR, and arterial levels of ET-1, insulin, glucagon, and glucose as well as SGO before and up to 30 min after diclofenac and at 20 min of ET-1 infusion (50 min after diclofenac)

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Postdiclofenac</th>
<th>ANOVA* (including basal and postdiclofenac data)</th>
<th>ET-1</th>
<th>Student's Paired t-Test (ET-1 vs. 30 min postdiclofenac)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>8</td>
<td>58±2</td>
<td>57±2</td>
<td>56±4</td>
<td>58±2</td>
</tr>
<tr>
<td>$\dot{V}O_2$, ml/min</td>
<td>4</td>
<td>261±8</td>
<td>260±9</td>
<td>258±12</td>
<td>255±13</td>
</tr>
<tr>
<td>(a-pa)$_O_2$, ml/l</td>
<td>4</td>
<td>45±2</td>
<td>46±2</td>
<td>49±3</td>
<td>44±2</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>4</td>
<td>5.89±0.32</td>
<td>5.65±0.35</td>
<td>5.45±0.35</td>
<td>5.88±0.33</td>
</tr>
<tr>
<td>BF$_{Spl}$, l/min</td>
<td>8</td>
<td>1.36±0.07</td>
<td>1.17±0.06</td>
<td>1.21±0.09</td>
<td>1.30±0.07</td>
</tr>
<tr>
<td>RBF, l/min</td>
<td>8</td>
<td>1.47±0.09</td>
<td>1.29±0.09</td>
<td>1.28±0.08</td>
<td>1.25±0.08</td>
</tr>
<tr>
<td>$O_2$renal, ml/min</td>
<td>6</td>
<td>65±3</td>
<td>60±3</td>
<td>62±4</td>
<td>63±3</td>
</tr>
<tr>
<td>$O_2$$_{Spl}$, ml/min</td>
<td>4</td>
<td>20±2</td>
<td>22±2</td>
<td>19±2</td>
<td>19±1</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>8</td>
<td>92±2</td>
<td>96±3</td>
<td>94±35</td>
<td>93±3</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>4</td>
<td>14±1</td>
<td>13±1</td>
<td>12±1</td>
<td>14±1</td>
</tr>
<tr>
<td>SVR, mmHg.min⁻¹.l⁻¹</td>
<td>4</td>
<td>16.2±1.3</td>
<td>17.5±1.6</td>
<td>17.7±1.6</td>
<td>16.4±1.3</td>
</tr>
<tr>
<td>PVR, mmHg.min⁻¹.l⁻¹</td>
<td>4</td>
<td>0.80±0.08</td>
<td>0.70±0.13</td>
<td>0.80±0.07</td>
<td>0.92±0.14</td>
</tr>
<tr>
<td>VR$_{Spl}$, mmHg.min⁻¹.l⁻¹</td>
<td>8</td>
<td>66.8±3.3</td>
<td>79.5±4.04</td>
<td>76.4±4.98</td>
<td>71.8±3.95</td>
</tr>
<tr>
<td>RVR, mmHg.min⁻¹.l⁻¹</td>
<td>8</td>
<td>63.0±3.3</td>
<td>74.6±4.64</td>
<td>74.2±5.44</td>
<td>75.8±5.24</td>
</tr>
<tr>
<td>Arterial concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET-1, pmol/l</td>
<td>8</td>
<td>5.53±0.36</td>
<td>5.60±1.01</td>
<td>5.91±1.09</td>
<td>6.75±0.77</td>
</tr>
<tr>
<td>Insulin, µU/ml</td>
<td>8</td>
<td>7.33±1.22</td>
<td>7.34±1.11</td>
<td>7.77±1.35</td>
<td>4.93±0.81</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>8</td>
<td>67.3±4.3</td>
<td>65.9±5.1</td>
<td>69.4±4.7</td>
<td>54.4±4.1</td>
</tr>
<tr>
<td>Glucose, mmol/ml</td>
<td>8</td>
<td>5.00±0.17</td>
<td>5.08±0.14</td>
<td>5.04±0.14</td>
<td>5.00±0.14</td>
</tr>
<tr>
<td>SGO, mmol/min</td>
<td>8</td>
<td>0.85±0.13</td>
<td>0.68±0.07</td>
<td>0.68±0.105</td>
<td>0.68±0.07</td>
</tr>
</tbody>
</table>

Values are means SE; n, no. of subjects. HR, heart rate; $\dot{V}O_2$, O$_2$ uptake; (a-pa)$_O_2$, arterial-pulmonary arterial O$_2$ difference; CO, cardiac output; BF$_{Spl}$, splanchnic blood flow; RBF, renal blood flow; $O_2$$_{Spl}$, splanchnic O$_2$ uptake; O$_2$renal, renal O$_2$ uptake; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; VR$_{Spl}$, splanchnic vascular resistance; RVR, renal vascular resistance; ET-1, endothelin-1; SGO, splanchnic glucose output; NS, not significant. *Repeated-measures design including basal value and values 10, 20, and 30 min postdiclofenac, followed by Fisher protected least-significant difference test. Significantly different from basal values; †P < 0.01; ††P < 0.001; ‡P < 0.05.

Fig. 1. Comparison of effects of endothelin-1 (ET-1) infusion with and without (controls, open bars) prior blockade of cyclooxygenase by diclofenac (control values are taken from Ref. 2). Left: *** and * indicate significantly different from basal value (P < 0.001 and P < 0.05, respectively) according to ANOVA, repeated measures for the time points before and up to 30 min after diclofenac followed by Fisher paired least significant difference test. Values at 20 min of ET-1 are compared with values 30 min postdiclofenac or basal value in the controls, according to Student’s paired t-test. Right: values at 20 min of ET-1 infusion with and without (controls) prior blockade expressed in percentage of basal value. P value indicates difference between groups based on Student's unpaired t-test.
Effects of ET-1 Infusion

Effects of ET-1 Infusion

Arterial levels of plasma ET-1 and catecholamines.
The arterial ET-1 level was 5.53 ± 0.36 pmol/l in the
basal state and unchanged at 30 min after diclofenac
(6.75 ± 0.77 pmol/l). Neither epinephrine nor norepi-
nephrine had changed from basal values (0.13 ± 0.04
and 1.02 ± 0.07 nmol/l, respectively) at 30 min after
diclofenac administration (0.13 ± 0.04 and 1.07 ± 0.12
nmol/l, respectively).

Glucose, insulin, and glucagon (Table 1). Basal insu-
lin and glucagon concentrations were 7.33 ± 1.22
µU/ml and 67.3 ± 4.3 pmol/l, respectively, and did not
change after diclofenac administration. Arterial glu-
cose showed a transient small increase. Splanchnic
change after diclofenac administration. Arterial glu-
cose metabolism is vasodilatation in these vascular beds,
and renal vascular beds but was transient in the
splanchnic vascular bed, with a return to basal level
within 30 min after diclofenac (Fig. 1). Concomitant
with a rapid return of splanchnic blood flow, CO also
increased from 20 to 30 min and MAP had returned to
basal value at 30 min after diclofenac. The reversal of
the effect of diclofenac on splanchnic blood flow is
noteworthy, considering the long plasma half-life of
diclofenac (1–2 h), but it could be due to more rapid
elevation of diclofenac at the site of action. Another
possibility is other local compensatory mechanisms in
the splanchnic as opposed to the renal vascular bed.

PGI2 synthesis has been suggested to exert negative
feedback and suppress ET-1 release (11), suggesting
that an additional possible cause of the reduction in
blood flow after COx inhibition could be increased ET-1
release. The present responses to COx inhibition are
not what would be expected of an ET-1-mediated re-
sponse. Accordingly, our previous results with intrave-
rous ET-1 administration (0.2–4 pmol·kg−1·min−1)
have shown that the vasoconstrictor response is approxi-
ately twofold higher in the splanchnic than the renal
circulation (2, 4, 27). Furthermore, these suppressions
of splanchnic as well as renal blood flow still persisted
60 min after the ET-1 infusions (4, 27), in accordance
with the almost irreversible binding of ET-1 to its
receptors (15).

Nor is it likely that decreased NO production could
have been caused by COx inhibition because this would
be expected to result in a decreased inhibition of
preproendothelin-1 proteolysis and hence increased
ET-1 formation (6, 30), followed by increased plasma
levels of ET-1. In accordance with such a mechanism,
our previous results have shown that administration of
the endogenous NO synthase inhibitor Nω-monomethyl-
arginine is followed by increased pulmonary ET-1
release, prolonged splanchnic and renal vasoconstric-
tion, and significantly reduced response to exogenous
ET-1 (1). Had the effect of Nω-monomethyl-L-arginine
been mainly withdrawal of the inhibitory NO influence
on smooth muscle contraction, then the ET-1 response
would have been increased vasoconstriction.

The present renal vasoconstrictor response to diclo-
fenac still persisted 30 min after diclofenac. That this
effect was not ET-1 elicited is further supported by the
subsequent ET-1 infusion results demonstrating an
even more pronounced renal blood flow reduction (33 ±
3%) compared with those in our previous control sub-
jects (23 ± 2%, P < 0.02) (4, 27) who received ET-1 in
the same way (4 pmol·kg−1·min−1 for 20 min) as in the
present study (Fig. 1). The total decrease in renal blood
flow with COx inhibition and ET-1 infusion in the
present study was 43 ± 3% compared with the basal
value and was thus twofold higher than that previously
found with ET-1 alone (P < 0.01). Taken together with
the lack of changes in plasma ET-1 levels after COx
inhibition, and the same proportional increase in arte-
rial ET-1 levels with ET-1 infusion (12-fold) as previ-
ously reported (2, 27, 28), the results indicate that basal

DISCUSSION

Cardiovascular Effects

The administration of diclofenac caused rapid effects
on splanchnic and renal blood flows, indicating inhibi-
tion of constitutive COx. Reductions in splanchnic and
renal blood flows are in accordance with previous
results seen during continuous infusion with the COx
inhibitor indomethacin (20) and corresponded in the
present study to >75% of the simultaneous reduction in
CO, showing that these vascular beds were the major
determinants for the rise in SVR and MAP. The results
indicate that the net effect of basal arachidonic acid
metabolism is vasodilatation in these vascular beds,

Downloaded from http://jap.physiology.org/ by 12.20.33.2 on November 16, 2017
PGI₂ synthesis, as opposed to NO (1), does not suppress ET-1 synthesis.

The subsequent ET-1 infusion caused reductions in splanchic blood flow (38%), CO (13%), and increase in MAP (4%) of a magnitude similar to those previously reported for splanchic blood flow (34–42%) (4, 27), CO (14%) (28), and MAP (6–7%) (27, 28) with only ET-1 infusion administered in the same way as in the present study.

Metabolic Effects

In parallel with the rapid initial reduction in splanchic blood flow after COx blockade, there was a 24% drop in splanchic glucose output that still persisted after splanchic blood flow had returned to basal value (Table 1). This 15% glucose output reduction was consequently not secondary to the decreased splanchic blood flow. In addition, an up to fivefold increase in splanchic glucose output is seen despite >-50% reductions in splanchic blood flow during physical exercise (for further discussion and references, see Ref. 3).

As to the mechanism for the reduced splanchic glucose output, the levels of the glucoregulatory hormones insulin, glucagon, epinephrine, and norepinephrine were unchanged. Although the hormonal findings are in agreement with those reported by others in healthy subjects using indomethacin as a COx inhibitor (9), the others reported a simultaneous increase in splanchic glucose output (9). Attempts to explain the difference in splanchic glucose output can only be speculative. Interestingly, in vitro studies have shown that prostaglandins stimulate hepatic glycogenolysis (7), suggesting that our finding of reduced splanchic glucose output after diclofenac might be due to withdrawal of prostaglandin stimulation of glycogenolysis. ET-1, on the other hand, has been shown to stimulate glycogenolysis in perfused rat livers or rat hepatocytes (13, 25), whereas our studies with ET-1 infusion in healthy subjects have demonstrated reduced splanchic glucose output. The results illustrate the difficulties encountered when in vitro and in vivo data, as well as data from different species, are compared.

The ET-1 infusion after diclofenac administration did not cause a similar proportional decrease (50–55%) in splanchic glucose output, as previously found with only ET-1 infused in the same way as in the present study (2, 3) or at a rate of 0.2 pmol·kg⁻¹·min⁻¹ (42 ± 6%) (4). This could be because splanchic glucose output was already markedly reduced (to 0.68 mmol/l) before the ET-1 infusion. The splanchic glucose production at 20 min of ET-1 infusion was too low to maintain the arterial glucose level (Table 1), which fell. This was accompanied by a reduction in arterial insulin levels, as previously found with ET-1 infusion (2, 3). Similarly, arterial glucagon fell as previously reported (2, 3). Because these hormonal changes occurred to the same extent as previously reported, but with a much smaller effect on splanchic glucose output, the results suggest that ET-1 has a direct suppressive effect on glucagon release.

In summary, COx inhibition causes increased MAP mainly due to reductions in renal and splanchic blood flows, indicating a basal vasodilating effect mediated by PGI₂. The longer duration of renal blood flow suppression, demonstrating that the kidney is more susceptible to COx inhibition by diclofenac, suggests that the kidney is more dependent on PGI₂ synthesis for maintaining basal vascular tone. Compensatory mechanisms to counteract the effects of diclofenac seem to operate in the splanchic but not the renal vascular bed, rendering the latter more sensitive to circulating ET-1.

The results imply that whenever COx inhibitors such as diclofenac are administered to patients with elevated ET-1 levels, the potentiated effect of these two on renal blood flow has to be taken into consideration. This is especially important in pathophysiological conditions (with reduced renal blood flow) as seen in renal insufficiency (16).

This study was supported by Swedish Medical Research Council Grants 14X-10374 and 14X-6554, the King Gustav V and Queen Victoria Foundation, and the Clas Groschinsky Foundation.

Address for reprint requests: G. Ahlborg, Dept. of Clinical Physiology, Huddinge Univ. Hospital, SE-141 86 Huddinge, Sweden.

Received 30 December 1997; accepted in final form 18 June 1998.

REFERENCES

Circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor.


