Table 1S. Molecular Targets and Functions of Morphine Neural and Non-neural Systems

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Molecular target</th>
<th>Cell/organ</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>TLR-4, MD-2, Ceramide, S1P</td>
<td>Glial cells, spinal cord</td>
<td>Analgesic tolerance/hyperalgesia</td>
<td>1-4</td>
</tr>
<tr>
<td>Morphine</td>
<td>Increased Ceramide and S1P3</td>
<td>Endothelium</td>
<td>Vascular permeability</td>
<td>5</td>
</tr>
<tr>
<td>Morphine</td>
<td>’O₂’, ONOO⁻ oxidative stress, dopamine and serotonin release</td>
<td>CNS, mesangial cell; kidney glomerular epithelial cells</td>
<td>Protein nitrosylation, tolerance/hyperalgesia; proliferation and apoptosis</td>
<td>1,2,6-8</td>
</tr>
<tr>
<td>Morphine</td>
<td>COX-2/PGE2</td>
<td>Kidney, tumors, CNS</td>
<td>Glomerular enlargement, Vascular congestion, inflammation, neovascularization, tumor progression, hyperalgesia; CGRP release</td>
<td>9-11</td>
</tr>
<tr>
<td>Morphine</td>
<td>P38 MAPK, MAPK/ERK</td>
<td>CNS; endothelium</td>
<td>Hyperalgesia, tolerance and angiogenesis</td>
<td>12,13</td>
</tr>
<tr>
<td>Morphine</td>
<td>STAT3</td>
<td>Kidney; endothelium; cardiac; CNS</td>
<td>Cell proliferation, renal disease; cardioprotection; Morphine tolerance</td>
<td>14-17</td>
</tr>
<tr>
<td>Morphine</td>
<td>Inflammatory Cytokines</td>
<td>CNS</td>
<td>Pain, retinal neovascularization</td>
<td>18,19</td>
</tr>
<tr>
<td>Morphine</td>
<td>PDGF-BB/PDGFR-β</td>
<td>Human brain microvascular- and umbilical vein-endothelial cells; kidney</td>
<td>Vascular permeability, renal disease, mural cell recruitment to the vasculature in tumors</td>
<td>14,20-22</td>
</tr>
<tr>
<td>Morphine/</td>
<td>eNOS, iNOS,</td>
<td>CNS; kidney</td>
<td>Analgesic tolerance,</td>
<td>8,9,23,24</td>
</tr>
</tbody>
</table>
COX-2 (cyclooxygenase-2); CNS (central nervous system); eNOS (endothelial nitric oxide synthase); ERK (extracellular signal regulated kinase); HO-1 (hemoxygenase-1); iNOS (inducible nitric oxide synthase) MAPK (mitogen activated protein kinase); MD-2 (myeloid differentiation protein-2); PDGF (plateleted-derived growth factor); PDGFR-β (platelet-derived growth factor receptor-b); PGE-2 (prostaglandin E-2); S1P3 (sphingosine-1-phosphate receptor 3); STAT3 (signal transducer and activator of transcription 3); TLR-4 (toll like receptor-4).

References:


