Supplemental Table.1 Published preclinical research studies of progesterone use in adult traumatic brain injury

| Author | Model | Dose[i] | Outcome |
|---|---|---|---|
| Roof et al, 1992 (96) | MFC,<br>Adult M and F rats | P 4 mg/kg x 2d | ↓ edema at 3d post TBI (with P up to 24h)<br>Best with earlier P |
| Roof et al, 1993 (15) | MFC,<br>Adult F (OVX) rats | E implants vs. P 4 mg/kg x 6d | ↓ edema E + P, P alone; no change E alone |
| Roof et al, 1996 (10) | MFC,<br>Adult M and F rats | P 4 mg/kg x 7d | ↓ edema 6h to 3d; no change at 7d |
| Roof et al, 1997 (9) | MFC,<br>Adult M rats | P | ↓ 8-isoPGF 2α at 24, 48 and 72h |
| Galani et al, 2001 (97) | MFC,<br>Adult M rats | P 4 mg/kg x 3d vs. 5d | ↓ edema at 6d post TBI, 5d>3d |
| Wright et al, 2001 (17) | MFC,<br>Adult M rats | P 4 mg/kg x 1d | ↓ edema at 48h post TBI |
| Shear et al, 2002 (98) | MFC,<br>Adult M rats | P 4 mg/kg x 3d vs. 5d | ↓ LV, cell loss, 5d>3d<br>↑ MWM, ↓ sensory neglect with 5d only |
| Goss et al, 2003 (18) | MFC,<br>Adult M rats | P 8/16/32 mg/kg x 5d | ↑ MWM, ↓ thigmotaxis with P8, P16<br>No effect on LV |
| Djebaili et al, 2004 (99) | MFC,<br>Adult M rats | P 16 mg/kg vs. AP 4/8/16 mg/kg x 5d | ↓ C-3 activity at 1d with P16, AP8, AP16<br>↓ DNA fragmentation at 1d with AP16<br>↓ LV at 19d with P16, AP8, AP16 |
| Grossman et al, 2004 (100) | MFC,<br>Adult M rats | P 4 mg/kg x 5d | ↓ edema with P<br>↑ macrophages/activated microglia |
| He, Restor. Neurol.Neurosci 2004 (101) | MFC,<br>Adult M rats | AP 4 mg/kg vs. Epi AP 4 mg/kg x 5d | ↑ MWM, ↓ LV at 7d AP; no change Epi AP |
| He, Exp.Neurol. 2004 (102) | MFC,<br>Adult M rats | P 8 mg/kg vs. AP 4 mg/kg x 5d | ↓ IL-1β, TNFα at 3h with P, AP |
| Cutler et al, 2005 (19) | MFC,<br>Adult M rats | P 16 mg/kg x 7d +/- taper | ↑ anxiety - P taper<br>↓ apoptotic, inflammatory markers + P taper |

| Author | Model | Dose | Outcome |
|---|---|---|---|
| Djebaili et al, 2005 (33) | MFC,<br>Adult M rats | P 16 mg/kg vs. AP 4/8/16 mg/kg x 5d | ↓ C-3, Bax proteins at 1d with P, AP<br>↓ DNA fragmentation at 1d with P, AP<br>↓ size GFAP and astrocytes at 1d with P, AP<br>↑ MWM at 19d with P, AP8 |
| Jones et al, 2005 (103) | ACI,<br>M mice | P 8 mg/kg IP at 2', 6h, 24h | ↓ LV at 48h post TBI with P<br>↑ MWM at 15-20d with P<br>No change in edema or expression of pro-inflammatory cytokine genes with P |
| O'Connor et al, 2005 (104) | Impact Acceleration Model,<br>Adult M and F (OVX) rats | E 33.3 μg/kg vs. P 1.7 mg/kg SC x 1 at 30' | ↓ BBB penetration with E, P<br>↓ edema at 5h, 72h with E, P |
| Pettus et al, 2005 (105) | MFC,<br>Adult M rats | P 16 mg/kg x 2d | ↓ NFKβ and complement C3 at 48h with P<br>No effect on GFAP |
| Yao et al, 2005 (13) | L-FPI,<br>Adult M rats | P 4 mg/kg x 6d | ↓ pro-apoptotic Bax/Bad proteins with P<br>↑ anti-apoptotic Bcl-2/Bcl-xl protein with P |
| Cutler, Exp.Neurol. 2005 (19) | MFC,<br>Adult M rats | P 16 mg/kg x 6d +/- taper | ↓ sensory neglect, ↑ locomotor activity + P taper<br>↓ LV + P taper<br>↑ GFAP reactivity - P taper |
| Cutler, Pharmacol. Biochem.Behav. 2006 (39) | MFC,<br>Adult M rats | P 16 mg/kg x 6d + taper vs. implant | ↓ anxiety, ↑ locomotor activity with implants |
| Guo et al, 2006 (25) | MFC,<br>Adult M rats | P 16 mg/kg x 2d | ↓ edema with P<br>AQP4 unchanged at 24h, ↓ at 72h in lateral ventricles and peri-contusion, ↑ at 72h in 3rd ventricle |
| Robertson et al, 2006 (8) | CCI,<br>F (OVX) rats | Low & High P implant7d prior to TBI | ↑ mitochondrial RCR at 1h with low P<br>↓ HC neuronal loss: |

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|---|---|---|---|
| | | | CA1, CA3 with low P<br>CA3 only with high P<br>No change in LV with either low or high P |
| Cutler et al, 2007 (24) | MFC,<br>Aged adult M rats | P 8/16/32 mg/kg x 3d | ↑ locomotor activity at 72h with P16<br>↓ edema at 48h with P16<br>↓ inflammatory markers with P8, P16<br>↓ apoptosis with P16 |
| O'Connor et al, 2007 (7) | Impact Acceleration Model,<br>Adult M and F (OVX) rats | P 1.67 mg/kg SC q24h x 9d | ↑ motor/cognitive function with P (M, F)<br>↓ C-3 reactivity with P (M only)<br>↓ dead/dying neurons with P (M only)<br>↓ axonal injury with P (M, F) |
| Pan et al, 2007 (23) | TBI model,<br>Rats | P | ↓ NFK β, TNF α with P<br>↓ edema, ↓ LV, ↑ neuro scores with P |
| VanLandingham et al, 2007 (106) | MFC,<br>Adult M rats | P 16 mg/kg vs. AP 8 mg/kg x 3d | ↑ CD55 at 24-72h with P, AP |
| Chen, Ann.Clin.Lab.Sci. 2008 (4) | CCI,<br>Adult M rats | P 16 mg/kg x 5d | ↓ TLR's, NFK β, IL-1β, TNFα, IL-6 with P<br>↓ TUNEL cells with P |
| Chen, J.Surg.Res. 2008 (107) | CCI,<br>Adult M rats | P 16 mg/kg x 5d | ↓ gut IL-1β, TNFα, ICAM-1 with P<br>No change in gut IL-6 with P<br>↓ gut apoptosis with P |
| Gilmer et al, 2008 (108) | CCI,<br>Adult M rats | P 8 vs. 16 mg/kg (at 15', 6h, q24h x 3d) vs. P 8 mg/kg + taper | No effect on edema at 3d<br>No effect on LV at 7d |
| VanLandingham et al, 2008 (109) | MFC,<br>Adult M rats | P 16 mg/kg vs. AP 8 mg/kg x 3d | ↑ procoagulants (thrombin, fibrinogen, coagulation factor XIII) with P<br>↑ anticoagulants (t-PA) with AP |
| Wright et al, 2008 (110) | MFC,<br>Adult M rats | MPA 4 vs. 16 mg/kg | ↓ edema with both doses MPA<br>No change behavior with either dose |

| Author | Model | Dose | Outcome |
|---|---|---|---|
| Kasturi et al, 2009 (111) | MFC,<br>Young and aged F (OVX) rats | P 16 mg/kg x 1d | ↓ edema in both ages with P<br>↑ P serum levels in old rats at 6h post TBI |
| Sayeed et al, 2009 (112) | CCI & MCAO,<br>Adult M rats | P and AP | ↓ mtPTP currents with AP, but not P<br>↓ Cyt c release with AP<br>↓ mitochondrial Cyt c at 24h post CCI, MCAO with AP>P |
| Shahrokhi et al, 2010 (113) | Marmarou weight drop,<br>Adult F (OVX) rats | P 8 mg/kg vs. E 1 mg/kg IP at 30' | ↓ brain edema at 24h with P, E<br>↓ ICP at 4h, 24h with P, E<br>↑CPP at 24h with P, E<br>↑ neurologic score with E only (not P) |
| Anderson et al, 2011 (114) | CCI,<br>Adult M rats | P 10 vs. 20 mg/kg IP at 4h, q12h x 3d | 24h: low P < 20% high P (DNA damage response)<br>72h: high P > 2 x low P (genes regulating inflammatory response and apoptosis)<br>7d: low P > high P (positive regulation of cell proliferation, innate immune response, anti-apoptosis, and blood vessel remodeling) |
| Barha et al, 2011 (115) | MFC,<br>Adult M rats | P 16 mg/kg x 7d (+ taper) + BrdU 200 mg/kg IP x1 at 48h | P after TBI normalizes the levels of cell proliferation and cell death in the dentate gyrus of the hippocampus |
| Cekic et al, 2011 (116) | CCI,<br>Aged M rats | P 16 mg/kg in VDH deficient rat vs. VDH normal rat x 3d | ↑ brain inflammation in VDH deficient rat<br>↓ benefits of P treatment in VDH deficient rat<br>Reversible if deficiency is corrected |
| Grossman et al, 2011 (117) | MFC,<br>Adult M rats | P 4 mg/kg x 5d | No change in behavior post TBI with P<br>↓ LV at 9d with P |
| Hua et al, 2011 (118) | MFC,<br>C57BL/6J mice | P 16 mg/kg IP at 1h, 6h<br>Brain tissue at 24h | No down-regulation of ↑ TLRs or their adaptor proteins with P |

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|---|---|---|---|
| Khaksari et al, 2011 (119) | Marmarou weight drop,<br>Adult F (OVX) rats | E 33.3 μg/kg vs. 1 mg/kg IP at 30'<br>P 1.7 vs. 8 mg/kg IP at 30' | ↑ edema with E1+P2 > E1<br>↓ E2 inhibitory effect on edema with P<br>↓ E1, E2 inhibitory effect on Evans blue content with E1+P1 and E2+P2<br>↓ IL-1β with E1, E2; E2+P2 > E2<br>↑ TGF-β with P or E alone<br>↓ TGF-β with P+E |
| Wali et al, 2011 (120) | CCI,<br>Aged M rats | P 16 mg/kg x 7d (+ taper) | ↑ functional outcomes with P<br>No effect on LV with P |
| Cekic et al, 2012 (121) | CCI,<br>Adult M rats | P 16 mg/kg x 7d (+ taper) | ↓ proNGF at 24h, 7d<br>↓ proBDNF, ↓ BDNF receptor TrkB<br>↑ mature NGF at 72h |
| Hua et al, 2012 (122) | MFC,<br>Adult M rats | P 16 mg/kg x 7d (+ taper)<br>+ VDH 1/2.5/5 μg/kg IP at 1h | ↑ preservation of spatial and reference memory with P + VDH > P alone<br>↑ GFAP reactions up to 21d with P+ low VDH |
| Li et al, 2012 (123) | CCI,<br>Aged M rats | P 16 mg/kg x 14d | ↑ neuro outcomes, ↑circulating EPC<br>↑ CD34, CD31 + cells and vessel density |
| Shahrokhi et al, 2012 (124) | TBI,<br>Adult F (OVX) rats | E 33.3 μg/kg vs. 1 mg/kg,<br>P 1.7 vs. 8 mg/kg | ↓ brain water content with E, P groups |
| Sarkaki et al, 2013 (125) | Marmarou weight drop,<br>Adult F (OVX) rats | E 33.3 μg/kg vs. 1 mg/kg IP at 30'<br>P 1.7 vs. 8 mg/kg IP at 30' | ↑ IL-1β at 6h with E2, P1<br>↓ IL-1β at 24h with E1, E2<br>↓ IL-6 at 6h with P2; at 24 h with P1, E1<br>↓ TNFα at 6h with P2<br>↑ TNFα at 24 h with E2<br>↑ TGFβ at 6h with E, P<br>↓ TGFβ with 24h with E1 |

ACI, aseptic cryogenic cerebral injury; AP, allopregnanolone; AQP4, aquaporin-4; BBB, blood brain barrier; BrdU, bromodeoxyuridine; C-3, caspase-3; CCI, controlled cortical impact; CPP, cerebral perfusion pressure; Cyt c, cytochrome c; E, 17-β estradiol; EPC, endothelial progenitor cells; Epi AP, epiallopregnanolone; F, female; GFAP, glial fibrillary acidic protein; HC, hippocampus; ICAM-1, intercellular adhesion molecule-1; ICP, intracranial pressure; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IP, intra-peritoneal; 8-isoPGF 2α, 8-isoprostaglandin F2α; L-FPI, lateral fluid percussion brain injury; LV, lesion volume; M, male; MCAO, middle cerebral artery occlusion**;** MFC, medial front cortex contusion; MPA, medroxyprogesterone; mtPTP, mitochondrial permeability transition pore; MWM, Morris water maze; NFKβ, nuclear factor kappa beta; OVX, ovariectomized; P, progesterone; proBDNF, pro brain derived neurotrophic factor; proNGF, pro nerve growth factor; RCR, respiratory control ratio; SC, sub-cutaneous; TBI, traumatic brain injury; TGF-β, transforming growth factor beta; TLR, toll-like receptors; TNF α, tumor necrosis factor alpha; t-PA, tissue type plasminogen activator; TrkB, tropomyosin receptor kinase B; TUNEL, terminal deoxynucleotidyl transferase mediated dUTP nick end-labeling; VDH, 1,25-dihydroxyvitmin D3.

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[i] Unless specified, dose regimens of P and AP are those used in Stein's lab (1st injection IP at 1h, subsequent injections SC at 6h, 24h and Q24h for duration of the experiment)