### Kynurenine alterations and therapeutic implications in psychiatric disorders

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| Schizophrenia | • Elevated L-KYN and KYNA levels and TDO expression in the prefrontal cortex<sup>13</sup>.  
  • Elevated L-KYN and TDO expression in the anterior cingulate cortex<sup>1</sup>.  
  • Elevated KYNA levels in the CSF<sup>15</sup>.  
  • Plasma 3-HK level correlates with clinical severity in first episode patients, and predicts disease progression<sup>6</sup>.  
  • Elevated KYNA levels increase the activity of VTA DA-ergic neurons in vivo, in an NMDAR-dependent manner<sup>7-9</sup>.  
  • Subchronic elevation of KYNA in the rat brain models the alterations of amphetamine-evoked DA-ergic responses observed in schizophrenia<sup>9</sup>.  
  • Elevated KYNA level in the rat brain impairs contextual fear conditioning, context discrimination, stimulus processing, spatial working memory, sensory gating and prepulse inhibition<sup>10-14</sup>. | • Chronic neuroleptic treatments decrease brain KYNA levels in vivo<sup>15</sup>.  
  • Blocking the formation of KYNA improves cognitive performance in vivo<sup>16,17</sup>.  
  • Administration COX-2 inhibitors results in decreased KYNA formation in vivo<sup>19</sup> and shows benefit in some clinical trials<sup>15,20</sup>. |

| Major depression and related disorders | • Decreased L-KYN levels in the plasma of patients with MDD<sup>21</sup>.  
  • Decreased TPR and L-KYN levels in the plasma of patients with MDD<sup>22</sup>.  
  • Elevated IDO activity, decreased KYNA levels and neuroprotective ratio in the plasma of patients with MDD<sup>23</sup>.  
  • Increased density of QUIN-immunoreactive microglia in the cingulated cortex of patients with MDD<sup>24</sup>.  
  • Correlating neopterin and IDO activity accompanied by elevated L-KYN levels in the plasma of suicide attempter MDD patients<sup>25</sup>.  
  • Elevated IDO activity and decreased TRP levels in the plasma of adolescent MDD patients with melancholic features<sup>26</sup>.  
  • Elevated IDO activity and L-KYN levels in end-term pregnancy and early puerperium being significantly pronounced in patients with depressive symptoms<sup>27</sup>.  
  • Increased L-KYN levels in the anterior cingulate cortex of patients with BPD<sup>3</sup>.  
  • Increased density of TDO-immunoreactive microglia in the anterior cingulate cortex of patients with MDD and BPD<sup>3</sup>.  
  • Elevated KYNA levels in the CSF of euthymic patients with BPD<sup>28</sup>.  
  • Decreased TRP and KYNA levels in the plasma of manic BPD patients<sup>29</sup>.  
  • IFN-α treatment evokes depressive symptoms accompanied by increased IDO activity and L-KYN/KYNA ratio in the serum<sup>30</sup>, elevated QUIN and KYNA levels in the CSF<sup>31</sup>.  
  • UCMS in mice activates TRP breakdown in the periphery and evoke distinct kynurenine alterations between cortical and subcortical structures<sup>32,33</sup>. | • Inhibition of IDO activity abolishes depressive like behaviour induced by LPS<sup>34</sup> and BCG in vivo<sup>35</sup>.  
  • Common antidepressants inhibit TDO activity in vivo<sup>36-38</sup>. |

Abbreviations: 3-HK, 3-hydroxykynurenine; BCG, Bacille Calmette-Guérin; BPD, bipolar disorder; COX-2, cyclooxygenase -2; CSF, cerebrospinal fluid; DA, dopamine; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; KYNA, kynurenic acid; L-KYN, L-kynurenine; LPS, lipopolysaccharide; MDD, major depressive disorder; QUIN, quinolinic acid; TDO, tryptophan 2,3-dioxygenase; TRP, tryptophan; UCMS, unpredictable chronic mild stress; VTA, ventral tegmental area.

SUPPLEMENTARY INFORMATION

27. Maes, M. et al. Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. Life Sci. 71, 1837-1848 (2002).