

# Extracellular Mitochondrial ATP, Suramin, and Autism?

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A recent publication reported that pregnant mice injected with the viral-like material Poly(I:C) produced, as previously known, offspring that exhibit behavior reminiscent of autism; it also reported that therapy with the antipurinergic drug suramin, used to treat the African disease trypanosomiasis, blocked ATP (a purine)-dependent biochemical and behavioral changes in these mice.<sup>1</sup> The authors asserted that this represents a new theory of mitochondrial-derived purinergic chemicals leaking outside a cell and signaling danger to surrounding cells.<sup>1</sup> This is an exciting finding and may suggest an important role of extracellular ATP in autism. However, this theory is apparently contrary to numerous reports of dysfunctional mitochondria and reduced ATP in patients with autism.<sup>2,3</sup>

The release of mitochondrial molecules extracellularly is not new. Extracellular ATP was previously considered a universal alarm signal released from cells under stress and capable of affecting neighboring cells,<sup>4</sup> including mast cells.<sup>5</sup> Extracellular ATP was also reported to augment inflammatory brain disease,<sup>6</sup> microglial survival,<sup>7</sup> as well as trigger and maintain inflammation in asthmatic airways.<sup>8</sup>

Nevertheless the findings by Naviaux et al,<sup>9</sup> are supported by previous studies showing that extracellular mitochondrial material could be released from activated mast cells, unique immune cells involved in allergies and eczema.<sup>10</sup> Many patients with autism have food allergies<sup>11</sup> and allergic-like symptoms<sup>12,13</sup> suggesting mast cell activation.<sup>14,15</sup> A recent epidemiologic study of 92,642 children reported a strong correlation between atopic dermatitis (ie, eczema), attention deficit hyperactivity disorder, and autism.<sup>16</sup> Moreover, children with mastocytosis, a spectrum of diseases that present with skin allergies,

hyperactivity, and difficulty focusing,<sup>17</sup> appear to have a 5-fold higher prevalence of autism spectrum disorder (1 out of 10 children) than that reported for the general population.<sup>18</sup>

This extracellular mitochondrial material could induce an intense autoimmune reaction from other cells,<sup>19,20</sup> including augmentation of allergic responses,<sup>21</sup> and could lead to focal brain inflammation.<sup>22</sup> About 50% of this material contained ATP, the action of which could be blocked by purinergic receptor inhibitors. The clinical importance of these findings was the fact that DNA was elevated in young children with autism.<sup>23</sup> All findings in the study using suramin were based on the assumption that it is a specific antipurinergic drug.<sup>1</sup> However, suramin is nonspecific and can affect G-coupled receptors,<sup>24</sup> as well as inhibit mast cells secretion,<sup>5</sup> T cell proliferation,<sup>25</sup> and polymorphonuclear leukocyte bactericidal activity.<sup>26</sup>

The authors did not explain how an antipurinergic effect could prevent the behavioral changes in the poly (I:C) mouse model that had been shown to depend on interleukin (IL)-6 increase<sup>27</sup> and not to develop in IL-6 null mice,<sup>28</sup> unless suramin blocks the release or antagonizes the action of IL-6. One possibility might be that activation of purinergic receptors leads to IL-6 release that could be indirectly blocked by suramin as it is blocked by luteolin in microglia.<sup>29,30</sup> In fact, suranim can also block G-coupled receptors, ATPases,<sup>31</sup> and mast cells.<sup>32,33</sup> Given the fact that poly (I:C) maternal infection model does not occur in IL-6 knockout mice,<sup>28,34</sup> and that most of the IL-6 depends on mast cells,<sup>35</sup> one wonders if the actions of suramin

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reported are not due to antipurinergic actions as reported, but more due to effects on mast cells.<sup>22</sup>

The use of the term *therapy* in the title of the article<sup>1</sup> is unsuitable because we refer to therapy when the pathogenesis of a disease is known, unlike autism. This created unrealistic expectations from colleagues and patients. “Blocking purinergic receptors” or experimental “treatment” would have been more appropriate than “therapy” especially because mouse models poorly mimic inflammatory diseases in human beings.<sup>36</sup>

Suramin can induce severe urticarial reactions in more than 90% of patients and adrenal damage in about 50%; suramin can also impair renal function, induce blood dyscrasias, optic atrophy and peripheric neuritis.<sup>37</sup> It is also contraindicated in hepatic dysfunction.<sup>38</sup> Additional interactions with other drugs,<sup>39</sup> or with supplements commonly given to children with autism<sup>40</sup> may also occur.

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#### CONFLICTS OF INTEREST

Tufts University has filed on behalf of TCT the following US applications: No 61/405,414 (filed October 21, 2010) entitled “Extracellular mitochondria-based screening and treatment” and PCT/US11/57405 (filed October 21, 2011) entitled “Extracellular mitochondria-based screening and treatment”, as well as US 13/880,736 (filed October 21, 2013) entitled “Extracellular mitochondria-based screening and treatment.” The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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