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Overstimulation of the α_{1B}-adrenergic receptor causes a "seizure plus" syndrome

To the editor—Zuscik and colleagues[1] report transgenic mice with overexpression of the α_{1B}-adrenergic receptor (α_{1B}AR) leading to apoptotic neurodegeneration in α_{1B}-expressing domains including cerebral cortex, hypothalamus, thalamus and cerebellum. Moreover, their model showed a reduction of tyrosine hydroxylase immunoreactivity in the substantia nigra with a loss of neuronal cell bodies and axonal projections. Transgenic mice exhibited a terazosine- and L-DOPA–responsive parkinson-like motor disorder predominantly affecting gait in association with recurrent grand mal seizures and some degree of autonomic failure. The authors propose that both the behavioural and neuropathological phenotype displayed by α_{1B}AR transgenic mice are consistent with the autonomic (Shy–Drager) presentation of multiple system atrophy (MSA). We disagree with this conclusion. MSA is a neurodegenerative disorder that is dominated clinically by autonomic dysfunction and L-DOPA–unresponsive parkinsonism, or less commonly, cerebellar ataxia[2,3]. The term 'Shy–Drager syndrome' has been misused in the past to encompass not only MSA, but also Parkinson disease (PD) with autonomic failure[4]. It was therefore abandoned by a recent consensus conference on the clinical diagnosis of MSA (ref. 5). A seizure disorder, one of the key features of the transgenic mice model described by Zuscik and colleagues, does not occur in MSA (ref. 3). Furthermore, the pattern of brain lesions present in the transgenic mouse model (beginning in cortex, hypothalamus and cerebellum, then progressing with age to encompass all brain areas) is only partially consistent with the neuropathology of MSA that is characterized by neuronal cell loss and gliosis particularly involving putamen and substantia nigra (striatonigral degeneration) as well as pons, inferior olives and cerebellar cortex (olivopontocerebellar atrophy), and preganglionic sympathetic centres in the intermediolateral cell column of the spinal cord[6]. In contrast, cortex and hypothalamus are relatively spared. In addition, in MSA there is prominent subcellular pathology comprising α-synuclein–positive glial and neuronal cytoplasmic and nuclear inclusions, with a distribution selectively involving basal ganglia, supplementary and primary motor cortex, reticular formation, basis pontis, middle cerebellar peduncles and cerebellar white matter[6,7]. Together with Parkinson Disease and dementia with Lewy bodies, MSA is increasingly conceived as α-synucleinopathy[8]. Although Zuscik *et al.* briefly mention the presence of cytoplasmic inclusions in the discussion, they do not state whether MSA-like glial and/or neuronal α-synuclein inclusions were present in the transgenic brains. We therefore conclude that Zuscik *et al.* provide no convincing evidence for a transgenic mouse model of MSA and instead report an unusual 'seizure-plus' syndrome based on a neuronal multisystem degeneration with prominent cortical degeneration.

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Perez replies—Wenning and colleagues report that our transgenic model of systemically overexpressed α_{1B}-adrenergic receptors[1] is not an accurate model of MSA, and they suggest that the main features are those of a seizure phenotype. Though we do agree that seizures are uncommonly seen in MSA, the seizure phenotype is consistent with the lesions produced and may represent a mouse manifestation of MSA. The mouse cerebral cortex has a much higher α_{1B}-advenergic receptor density than humans which would explain the greater degeneration. Moreover, there are now several reports in humans of extensive cerebral cortex degeneration associated with MSA (refs. 8–10).

The main features of MSA include parkinsonism, autonomic dysfunction, cerebellar ataxia and degeneration mainly in the olivopontine areas, and corticospinal dysfunction. The diagnosis of possible MSA requires one criterion plus two features from separate other domains[5]. Although we have not investigated spinal dysfunction, the mice have the other three impairments. In the paper, we provide direct evidence of parkinsonism with locomotion dysfunction and corresponding histology of loss of dopaminergic termini in the substantia nigra. Although MSA patents are typically unresponsive to L-DOPA, 25% of MSA patents still respond. It is thought that varying extent of putaminal damage could be responsible for the differing motor response to L-DOPA in MSA patients[11]. Only one of our lines (and the most severely affected), the T1, responded to L-DOPA. We did not test if this response was refractory.

The rearing deficit and gait problems indicate cerebellar ataxia. Although we do not show the histology in our paper, we refer to the extensive degeneration in the cerebellum. The areas affected most severely are in the olivopontine regions and there is also Purkinje-cell loss, another criterion of MSA. The autonomic dysfunction was again referred to in the paper but the data will be presented elsewhere (manuscript submitted). Essentially, the mice have reproductive failure, weight loss in midlife, low sympathetic output (as measured by catecholamine and cortisol levels) and hypotension. The autonomic dysfunction is also consistent with the lesions shown in the paper that include instances in hypothalamus and locus coeruleus—degeneration that also occurs in MSA. Another feature of MSA are cytoplasmic occlusion bodies that localize to glial cells. We have seen cytoplasmic occlusions but have yet to test if they localize to glial.

The objection is perhaps a result of our presentation in the paper. As with any transgenic model, the requirement is to establish that the pathology is due to the transgene itself and not other factors. This is why we emphasized the degeneration in domains of the brain that highly express the α_{1B}AR at the expense of showing degeneration consistent with MSA.

Therefore, although we present his-