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# Expression of functional dopaminergic phenotype in purified cultured Müller cells from vertebrate retina

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ABSTRACT

Purified retina glial Müller cells can express the machinery for dopamine synthesis and release when maintained in culture. Dopamine is detected in cell extracts of cultures exposed to its precursor, L-DOPA. A large portion of synthesized dopamine is recovered in the superfusing medium showing the tendency of the accumulated dopamine to be released. Müller cells purified from developing chick and mouse retinas express L-DOPA decarboxylase (DDC; aromatic-L-amino-acid decarboxylase; EC 4.1.1.28) and the dopamine transporter DAT. The synthesis of dopamine from L-DOPA supplied to Müller cultures is inhibited by *m*-hydroxybenzylhydrazine, a DDC inhibitor. Dopamine release occurs via a transporter-mediated process and can activate dopaminergic $D_1$ receptors expressed by the glia population. The synthesis and release of dopamine were also observed in Müller cell cultures from mouse retina. Finally, cultured avian Müller cells display increased expression of tyrosine hydroxylase, under the influence of agents that increase cAMP levels, which results in higher levels of dopamine synthesized from tyrosine. A large proportion of glial cells in culture do express Nurr1 transcription factor, consistent with the dopaminergic characteristics displayed by these cells in culture. The results show that Müller cells, deprived of neuron influence, differentiate dopaminergic properties thought to be exclusive to neurons.


## 1. Introduction

The classical concept of glial cells in the nervous system implied that these cells were considered as supportive compartments towards neurons with morpho-structural and metabolic support. Recent evidences, however, have indicated that glial cells have a more active role in neuron physiology, participating in cellular communication within the nervous tissue (Newman and Reichenbach, 1996; Haydon, 2001; Fields and Stevens-Graham, 2002; Araque, 2006; Harada et al., 2000; de Melo Reis et al., 2008a; Puro et al., 1996; Lopez et al., 1997; Lamas et al., 2005; Biedermann et al., 1995; Schwartz et al., 1994; Kubrusly et al., 2005). Gliotransmitters as glutamate (Fellin et al., 2004), adenosine triphosphate (ATP) (Gordon et al., 2005; Newman, 2003) and D-serine (Panatier et al., 2006) have been implicated as mediators of glia–neuron cross-talk. Reciprocal interactions between glia and neurons have also been detected through gap junctions communication (Fróes et al., 1999). Glial cells also constitute a pool of multi-potent cell type that under appropriate conditions can give rise to new neurons or glia, in the mature as well as the developing nervous system (Noctor et al., 2001; Fischer and Reh, 2003).

Müller cells constitute the main glial cell type in the retina and span the tissue from the inner to the outer limiting membranes. Several functions have been attributed to these cells including structural and nutritional roles and removal of ions and neurotransmitters from the extra-cellular space (for a review, Bringmann et al., 2006; de Melo Reis et al., 2008b).

Recently we showed that aromatic amino acid decarboxylase, also known as L-DOPA decarboxylase (DDC), is expressed in the avian retinal tissue since embryonic day 6 (Kubrusly et al., 2003). Immunocytochemical analysis revealed that, at early developmental stages, this enzyme is concentrated near the outer plexyform layer (OPL), in a region that might be associated with the outer limiting membrane. The supply of L-DOPA to the embryonic tissue results in an expressive synthesis of dopamine

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