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EDITORIAL

# Nerve growth factor, D2 receptor isoforms, and pituitary tumors

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Dopamine (DA), by interacting with D2 receptors (D2R), exerts two major effects in the anterior pituitary: It inhibits prolactin (PRL) secretion and controls lactotrope cell proliferation, playing a role during pituitary development and tumorigenesis. In 1982, it was first reported that the spontaneous development of prolactinomas in old female rats was associated with the loss of hypothalamic DA neurons and that young female rats with estrogen-induced prolactinomas had damaged tuberoinfundibular DA neurons [1]. More recently, the development of transgenic mice lacking either the DA transporter (DAT) or the D2R pointed to the crucial role of DA in the control of lactotrope cell proliferation and in the pathogenesis of prolactinomas. Ablation of DAT, which physiologically controls DA function by mediating its re-uptake into nerve terminals, leads to a generalized dopaminergic hypertone, including increased DA overflow to the anterior pituitary. As a result, these mice developed hypopituitarism due to a defect in the proliferation and migration of lactotrope and somatotrope cells [2]. In D2R knockout mice, on the other hand, the control of hypothalamic DA over pituitary function was lost due to the lack of D2R expression, resulting in proliferation of lactotrope cells and in the development of prolactinomas in the older animals [3].

Several mechanisms have been invoked to explain the effects of DA on lactotrope cell proliferation and differentiation. Among these, an important synergistic interaction between DA and intrapituitary growth factors has been demonstrated. In particular, nerve growth factor (NGF), which is expressed in lactotrope cells and is released under DA control, promotes proliferation and differentiation of lactotrope cells during pituitary development in vitro [4]. Moreover, NGF plays a crucial role in the pathogenesis of prolactinomas. The majority of these adenomas maintain most of the characteristics of lactotrope cells including the expression of D2R, an observation that led to the development of D2R agonists as the most effective pharmacological tool to lower plasma PRL levels and to reduce the tumor size. A small percentage of patients, however, are insensitive to this therapy due to decreased D2R expression and/or D2R signaling. Analysis of the NGF system in cell lines obtained from human prolactinomas revealed that tumors that are sensitive to bromocriptine express both the D2R and an autocrine loop mediated by NGF, while those that are insensitive to D2R agonists lack both D2R and NGF secretion [4]. Escape from NGF control thus results in the development of prolactinomas that are refractory to the DA therapy. Interestingly, exposure of these tumors to NGF resulted in their differentiation into a lactotrope-like phenotype that expresses the D2R and recovers sensitivity to subsequent administration of D2R agonists [4].

The D2R exists as two isoforms, the D2S and D2L, that are generated by alternative splicing from the same gene and have similar pharmacological and biochemical profiles despite the presence or the absence of a stretch of 29 amino acids in the third intracellular loop. The D2S and D2L isoforms are both expressed in the brain and the pituitary, with the D2L isoform as the most abundant, and were thought for a long time to share the same functions. However, the generation of transgenic mice over-expressing either isoforms in the pituitary made it possible to demonstrate that the D2S, but not the D2L receptor, inhibits lactotrope cell proliferation, leading to pituitary hypoplasia [5]. More recent data indicated that the D2S, but not the D2L isoform, mediates apoptosis of lactotrope

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cells induced by DA and D2R agonists in an estrogen-dependent way [6]. Moreover, while D2S over-expression in transgenic mice resulted in a significant reduction of PRL mRNA and PRL plasma levels, D2L over-expression did not modify PRL mRNA and increases plasma PRL levels [5]. Taken together, these data suggest that, while D2S inhibits PRL synthesis and lactotrope cells proliferation and induces lactotrope cell apoptosis, the D2L may facilitate PRL release. Increasing the D2S/D2L ratio in lactotrope cells may thus force the system toward DA-mediated inhibition of proliferation, apoptosis, and inhibition of PRL synthesis. On this line, analysis of D2S and D2R expression in human prolactinomas showed that the decrease of D2R levels observed in non-responder tumors mostly involves the D2S rather than the D2L isoform, suggesting that in these tumors, the decreased D2S/D2L ratio is responsible for the insensitivity to D2R agonists [7]. In the paper published in this issue, Su et al. [8] report that exposure of the prolactinoma cell line GH3 to NGF differentially affects D2S and D2L expression. In particular, the D2S isoform appears to be more sensitive to NGF induction than the D2L isoform, leading to increased D2S/D2L ratio. As a result, NGF-treated GH3 cells respond to bromocriptine with decreased survival rate and apoptosis. These data thus point to the importance of the D2S/D2L ratio, rather than the total D2R expression, for the sensitivity of prolactinomas to DA agonists and suggest that NGF not only induces D2R expression, but also likely affects the mechanisms regulating D2R splicing.

Management of D2R agonist-resistant prolactinomas remains a therapeutic challenge. Although the observations summarized here may represent a breakthrough in the therapy of these tumors, a pharmacological therapy with NGF is hardly conceivable due to its pharmacokinetic and bioavailability limits. However, p75 was identified as the NGF receptor involved in the regulation of D2R expression and the Nuclear Factor-$\kappa$B (NF-$\kappa$B) as the transcription factor supporting D2R expression [9]. These findings may represent the basis for the development of small molecules that, by interacting with p75 or activating NF-$\kappa$B, may induce D2R expression in prolactinomas refractory to the therapy. Moreover, two binding proteins have been recently identified that regulate D2R pre-mRNA splicing [10], and this finding may open the way to a new potential approach directed to force the splicing toward the D2S isoform in a pituitary tumor-specific manner.

**Conflict of interest** None.

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