Dopamine receptor D2

Dopamine receptor D2, also known as D2R, is a protein that, in humans, is encoded by the DRD2 gene. After work from Paul Greengard's lab had suggested that dopamine receptors were the site of action of antipsychotic drugs, several groups (including those of Solomon Snyder and Philip Seeman) used a radiolabeled antipsychotic drug to identify what is now known as the dopamine D2 receptor.

The dopamine D2 receptor is the main receptor for most antipsychotic drugs. The structure of DRD2 in complex with the atypical antipsychotic risperidone has been determined.

There are ongoing clinical trials exploring the efficacy of dopamine receptor 2 (DRD2) inhibition against glioblastomas. He et al. examined potential molecular determinants of this efficacy.

The Cancer Genome Atlas (TCGA) glioblastoma database and other published mRNA profiles were used to analyze the DRD2 and EGFR expression pattern. In vitro and in vivo responses to DRD2 inhibitors were determined using patient derived xenograft (PDX) glioblastoma models. Immunohistochemical studies were performed on clinically annotated glioblastoma samples derived from patients treated with ONC201.

Analysis of clinical glioblastoma specimens derived from independent patient cohorts revealed an inverse correlation between EGFR and DRD2 mRNA expression, with implication that signaling mediated by these proteins shares overlapping functions. In independent panels of PDX glioblastoma lines, high EGFR expression was associated with poor in vitro and in vivo response to DRD2 inhibitors, including haloperidol and ONC201. Moreover, ectopic expression of a constitutively active EGFR, EGFRvIII, suppressed glioblastoma sensitivity to ONC201. DRD2 expression positively correlated with expression of rate-limiting enzymes for dopamine synthesis as well as dopamine secretion, suggesting contribution of autocrine DRD2 signaling. Analysis of specimens from patients treated with ONC201 (n = 15) showed an inverse correlation between the intensity of EGFR staining and clinical response. The median overall survival for patients with high and low EGFR staining was 162 and 373 days, respectively (p = 0.037).

High EGFR expression is a determinant of poor glioblastoma response to DRD2. This finding should inform future clinical trial designs [1)].

The predominant inhibitory receptors of GH secreting pituitary neuroendocrine tumor are somatostatin receptors (SSTRs) and D2 dopamine receptor (DRD2). The expression of these receptors is associated with the response to somatostatin analog and dopamine agonist treatment in human patients with acromegaly. The aim of this study was to describe pathological features of pituitaries from domestic cats with acromegaly, pituitary receptor expression, and investigate correlates with clinical data, including pituitary volume, time since diagnosis of diabetes, insulin requirement, and serum IGF1 concentration. Loss of reticulin structure was identified in 15 of 21 pituitaries, of which 10 of 15 exhibited acinar hyperplasia. SSTR1, SSTR2, SSTR5, and DRD2 mRNA were identified in the feline pituitary whereas SSTR3 and SSTR4 were not. Expression of SSTR1, SSTR2, and SSTR5 was greater in acromegalic cats compared with controls. A negative correlation was identified between DRD2 mRNA expression and pituitary volume. The loss of DRD2 expression should be investigated as a mechanism allowing the development of larger pituitary tumors [2)].

1)
He Y, Li J, Koga T, et al. Epidermal Growth Factor Receptor (EGFR) as a molecular determinant of glioblastoma response to dopamine receptor 2 (DRD2) inhibitors [published online ahead of print, 2020 Aug 24]. Neuro Oncol. 2020;noaa188. doi:10.1093/neuonc/noaa188
2)
Scudder CJ, Mirczuk SM, Richardson KM, Crossley VJ, Regan JTC, Gostelow R, Forcada Y, Hazuchova K, Harrington N, McGonnell IM, Church DB, Kenny PJ, Korbonits M, Fowkes RC, Niessen SJM. Pituitary Pathology and Gene Expression in Acromegalic Cats. J Endocr Soc. 2018 Oct 16;3(1):181-200. doi: 10.1210/js.2018-00226. eCollection 2019 Jan 1. PubMed PMID: 30620005; PubMed Central PMCID: PMC6316999.

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