This slide was courtesy of Dr. Bryan Roth, MD, PhD
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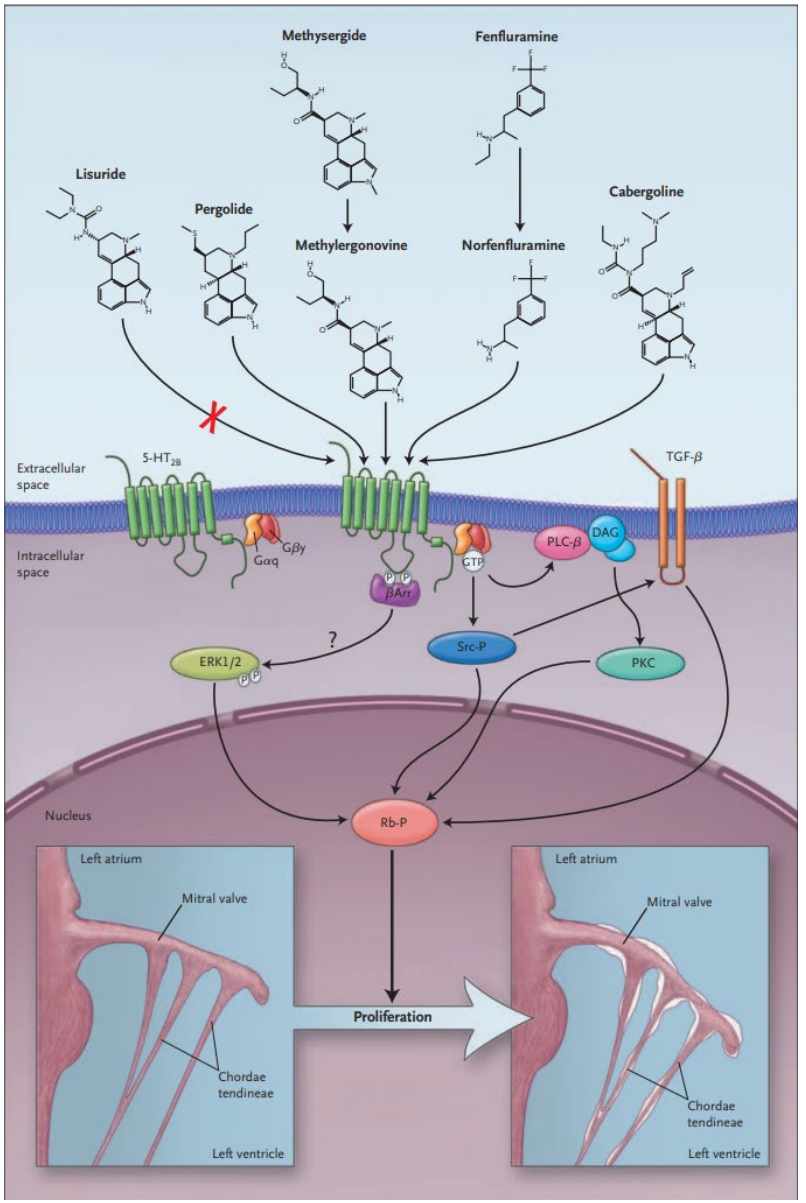
It will be viewable in the near future (see information about symposium and lecture title below) and shows that psychedelics, including psilocin, have high affinity for 5-HT2B receptors

NIH Psychedelics as Therapeutics Workshop.

Bryan Roth
The promise and peril of psychedelic pharmacology
January 12th
Videos will be posted in the near future

Discovery of 5-HT_{2B}-related toxicity: timeline

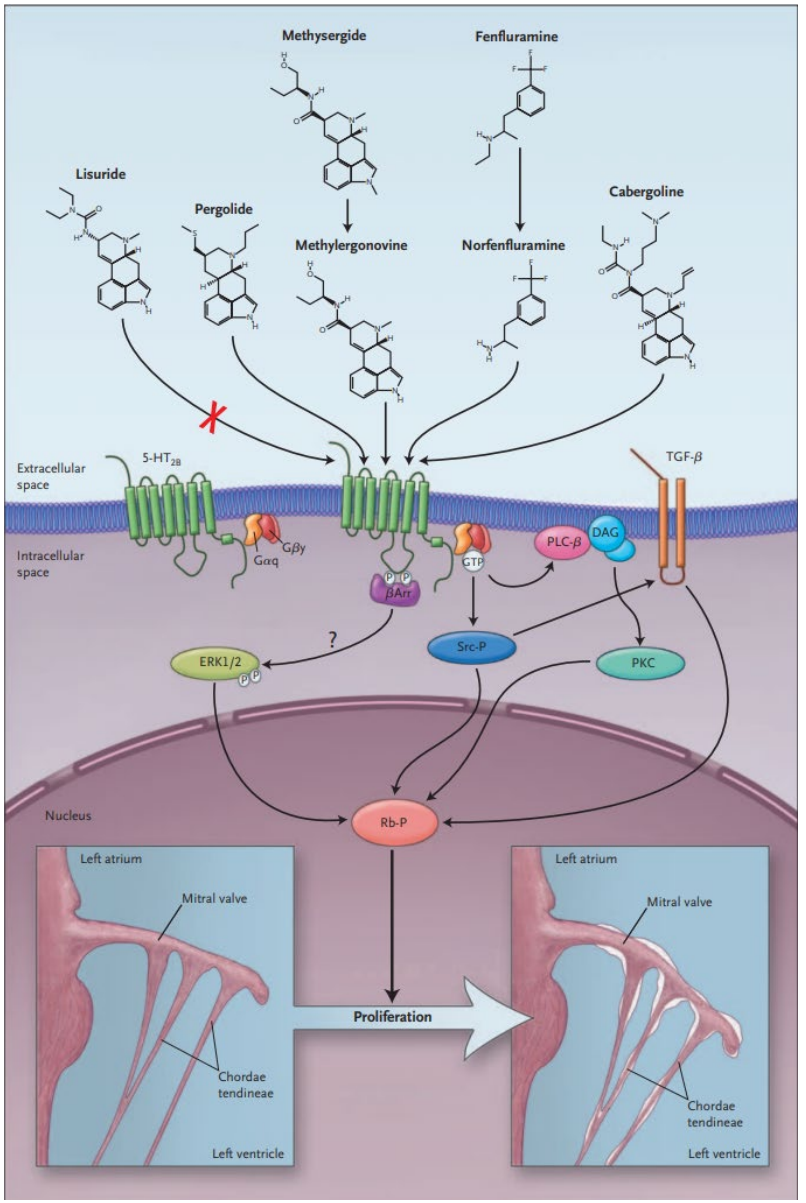
- Valvular heart disease was discovered to be associated with “fen-phen” in 1997
- In 2000, Bryan Roth and colleagues discovered that norfenfluramine, the active metabolite of fenfluramine, is a high affinity activator of 5-HT2B receptors → this is due to inappropriate mitogenic stimulation of normally quiescent valve cells, resulting in overgrowth



Roth, NEJM 2007

Discovery of 5-HT_{2B}-related toxicity: timeline

- Other FDA-approved drugs were screened in 2000, and two anti-Parkinson's medications pergolide and cabergoline, were found to be high affinity 5-HT2B agonists
- Prediction made at that time was that they (in contrast to other anti-Parkinson's meds) would be discovered to cause valvulopathy → this was convincingly established for both by 2007
  - Pergolide was removed from the market



Roth, NEJM 2007

Psilocin vs pergolide

- Psilocin has an EC50 at 5-HT2B – **2.37 nM** (Klein et al, 2021) – **58 nM** (Sard et al, 2005)
- Psilocin blood level with 6 mg dose reaches ~19 nM, 3 mg dose = ~10 nM; stays above ~5 nM for approximately 5 hours for both dosages
  → This suggests there will be significant activation of 5-HT2B receptors after a "microdose"

- Pergolide EC50 at 5-HT2B – **3.8 nM** (Gornemann et al, 2005) – **53 nM** (PDSP, Setola et al, 2003)
- Pergolide clinical doses that were associated with valvulopathy – <2 mg per day (OR = 3.1, Corvol, 2007)
  → Note the similar dosing and similar EC50
  → Risk increased linearly with pergolide cumulative dose – in other words, the higher the total amount of pergolide a person received (dose x time), the higher their risk of valvulopathy