History and Pharmacology of LDN

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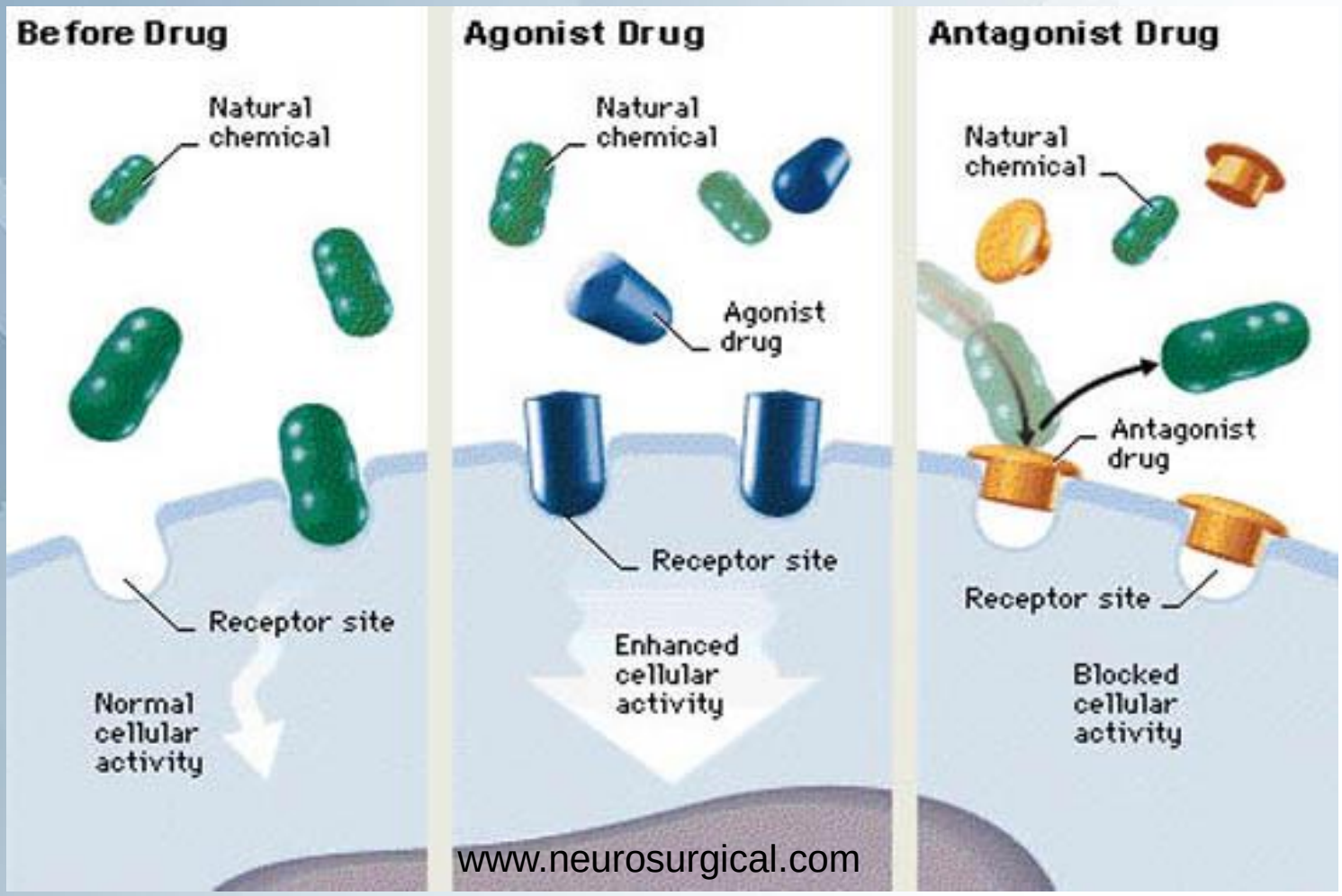
History and Pharmacology of LDN

Agonists and Antagonists



History and Pharmacology of LDN

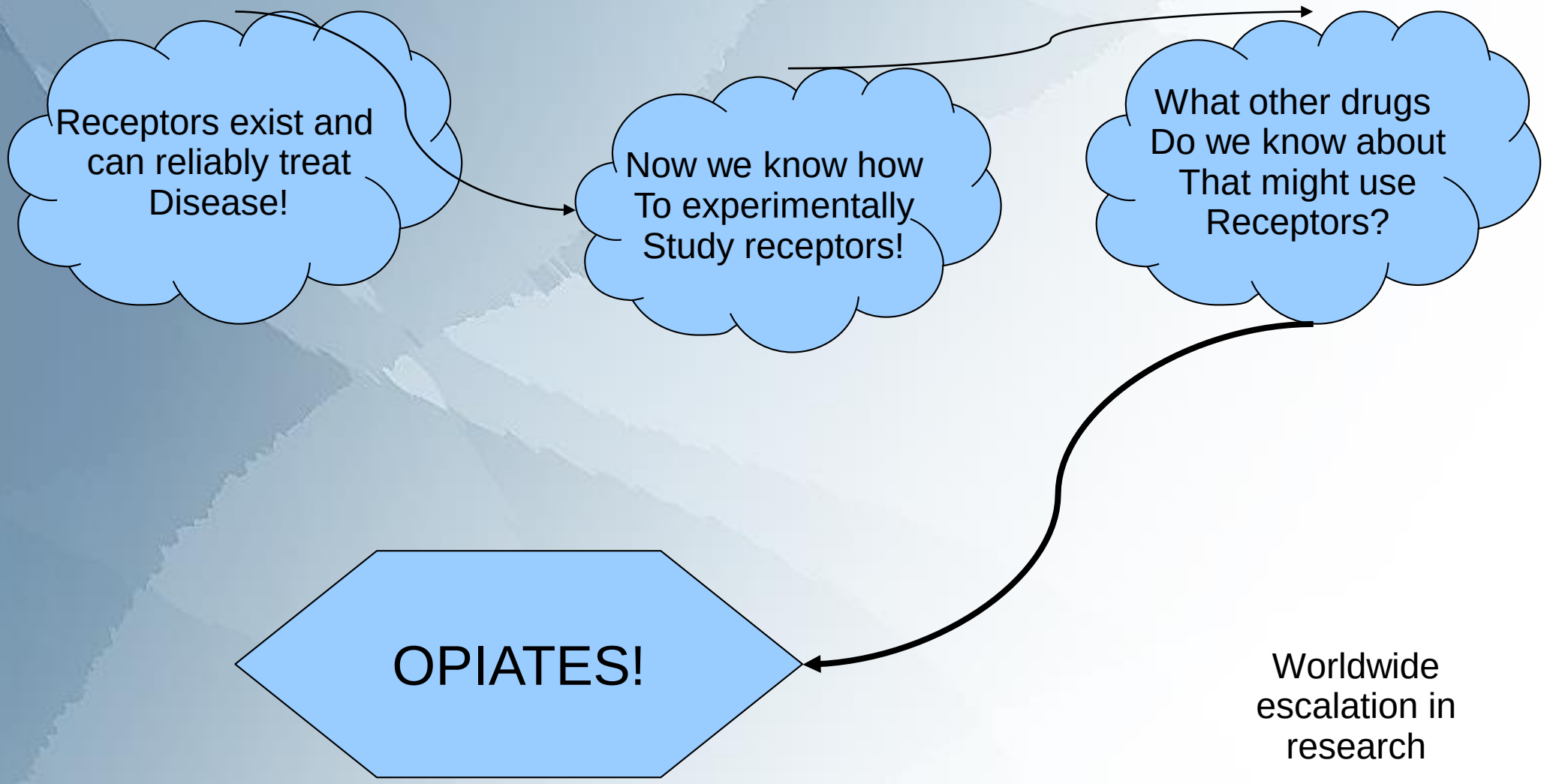
Antagonists Discovery

Sir James Black at the Rayne Institute in London, following the announcement that he was the joint winner of the Nobel prize in medicine © Associated Press

- Sir James W Black (1964)
- Adrenergic blocking drugs
- Important to be able to modify biological systems
- Discovery of proproanolol
- Nobel Prize 1988
- Millions of lives saved

History and Pharmacology of LDN

Scientific excitement!



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Where our story begins!

Presently she cast a drug into the wine of which they drank to lull all pain and anger and bring forgetfulness of every sorrow."

"Homer's Odyssey" 9th Century BC.

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Or does it?

The Archaic or Early Dynastic Period of Egypt immediately follows the unification of Lower and Upper Egypt c. 3100 BC. It is generally taken to include the First and Second Dynasties, lasting from the Protodynastic Period of Egypt until 2686 BC, or the beginning of the Old Kingdom.

History and Pharmacology of LDN

Laudanum / Papaverine

- In 1527 Paracelus (Swiss/German Doctor) alcoholic extract of opium.
- 1660 Dr Thomas Sydenham – widespread use by 1680.
- Every disease was “cured” by Laudanum.... and why not!

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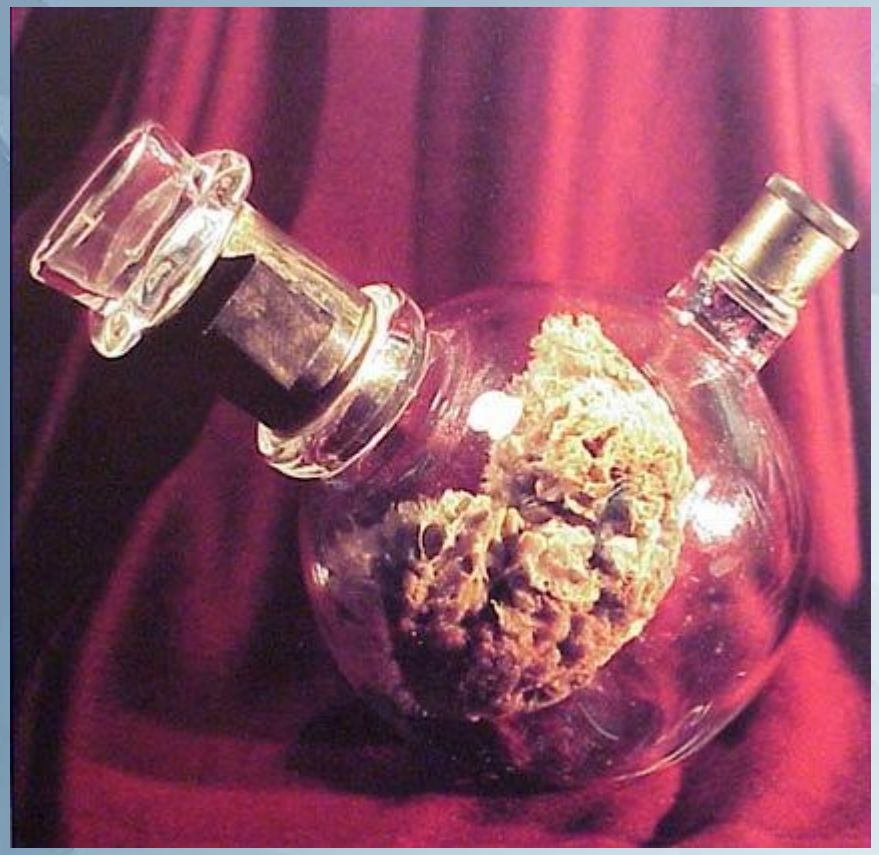
Big problems



- Overdose:
  - Breathing suppression
  - Death
- *Spongica Somniferum*
  - Ineffective
  - Too effecitve
  - Complications
  - Used until modern era

History and Pharmacology of LDN

Science progressed 1740-1830s

- Distillation
  - One “active principal”
  - More powerful?
  - Fewer side effects?
- Friedrich Serturner – Papaverine
  - Renamed morphine in 1806
  - Stronger, more reliable, standardised

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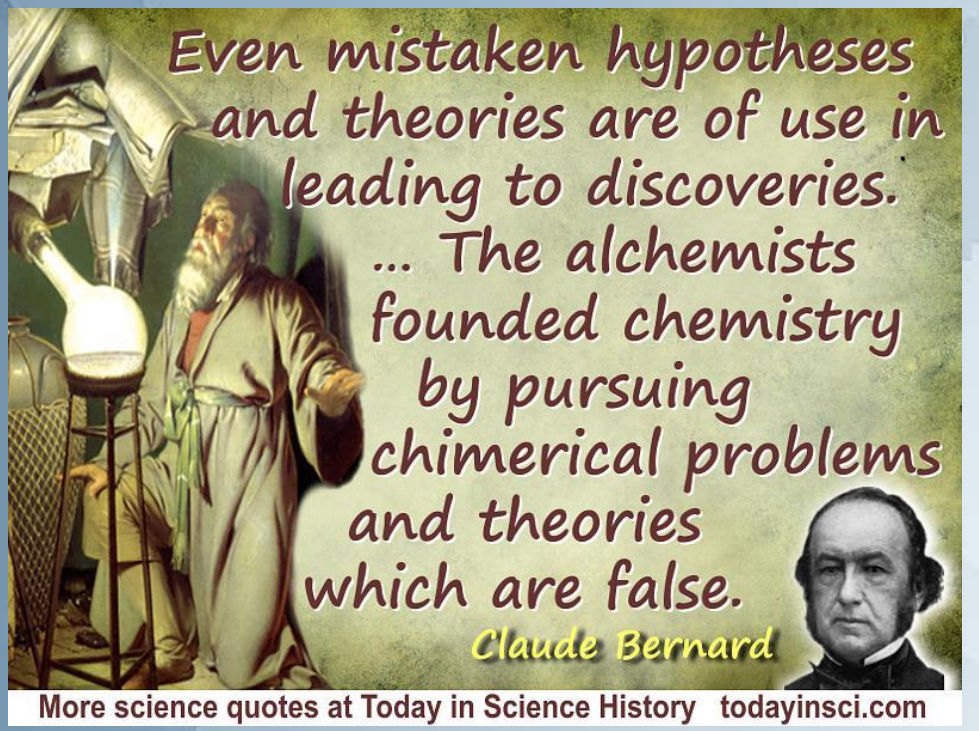
Claude Bernard 1850



- Animal experiments
  - Chloroform PLUS morphine was superior and safer
- Practice adopted worldwide
  - Over next 50 years still saw side effects and overdose problems.

History and Pharmacology of LDN

Modern big pharma begins! (1874)

Am. J. Ph.] 7 [December, 1901

BAYER Pharmaceutical Products

HEROIN—HYDROCHLORIDE

is pre-eminently adapted for the manufacture of cough elixirs, cough balsams, cough drops, cough lozenges, and cough medicines of any kind. Price in 1 oz. packages, $4.85 per ounce; less in larger quantities. The efficient dose being very small (1-48 to 1-24 gr.), it is

The Cheapest Specific for the Relief of Coughs

(In bronchitis, phthisis, whooping cough, etc., etc.)

WRITE FOR LITERATURE TO

FARBENFABRIKEN OF ELBERFELD COMPANY

SELLING AGENTS

P. O. Box 2160 40 Stone Street, NEW YORK

- *Charles Romley Alder Wright*
  - Variations on morphine made chemically, by adding acetyl groups.
  - The “New Morphine!”
  - “Safer” “More effective” “Cheaper” (all used to hearing these terms!)
  - Clearly incorrect!
  - Morphine and diamorphine widely used.

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- World War 1 – Disrupted trade & prevented sufficient supplies of morphine.

- Research began into chemical synthesis (SLOW)

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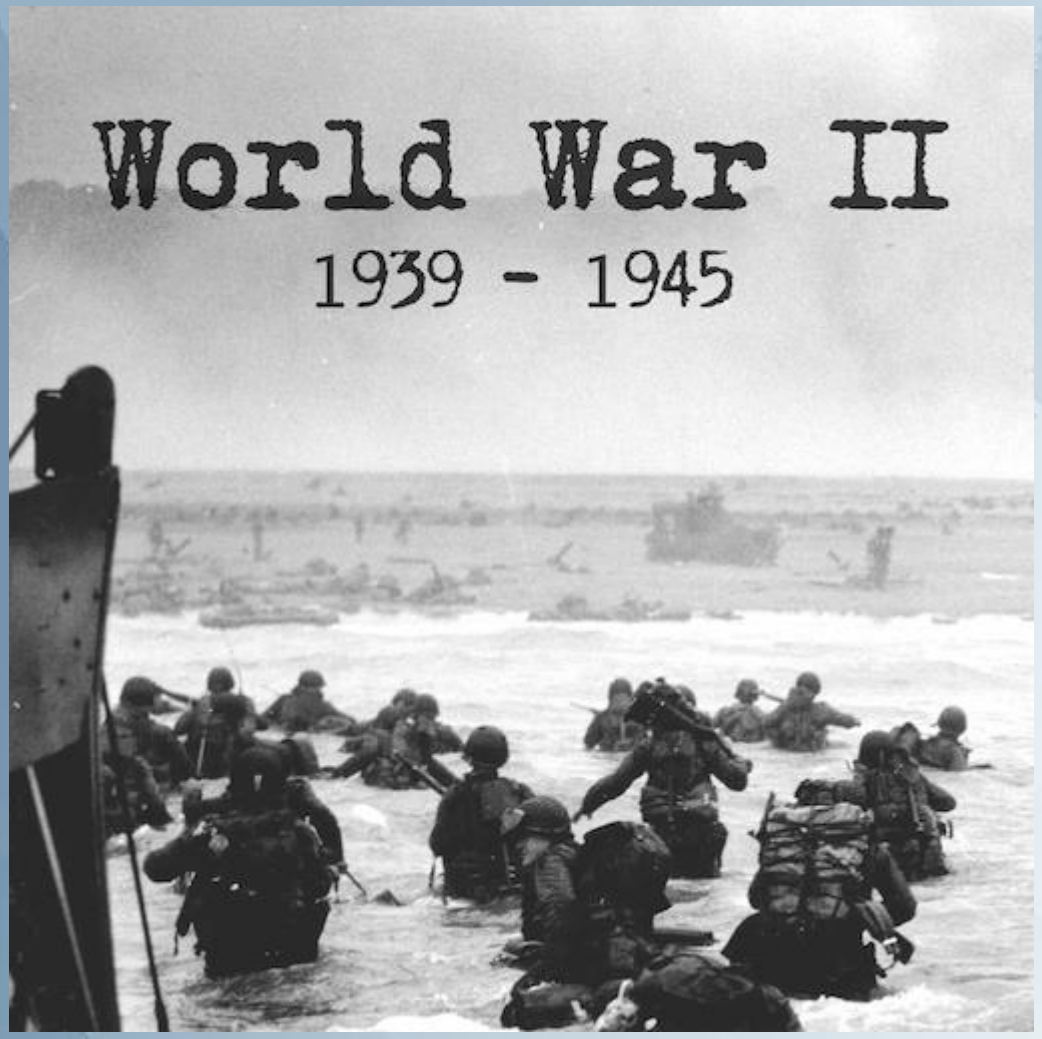

- By the start of WWII – no progress, but scientists had a new problem.

History and Pharmacology of LDN

Giant Pupil Man Eating Babies!

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Atropa-Belladonna

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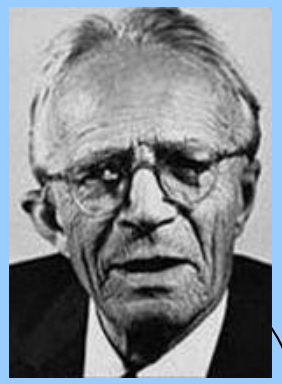
We need to synthesize Atropine!

1939
Dr Otto Eisleb

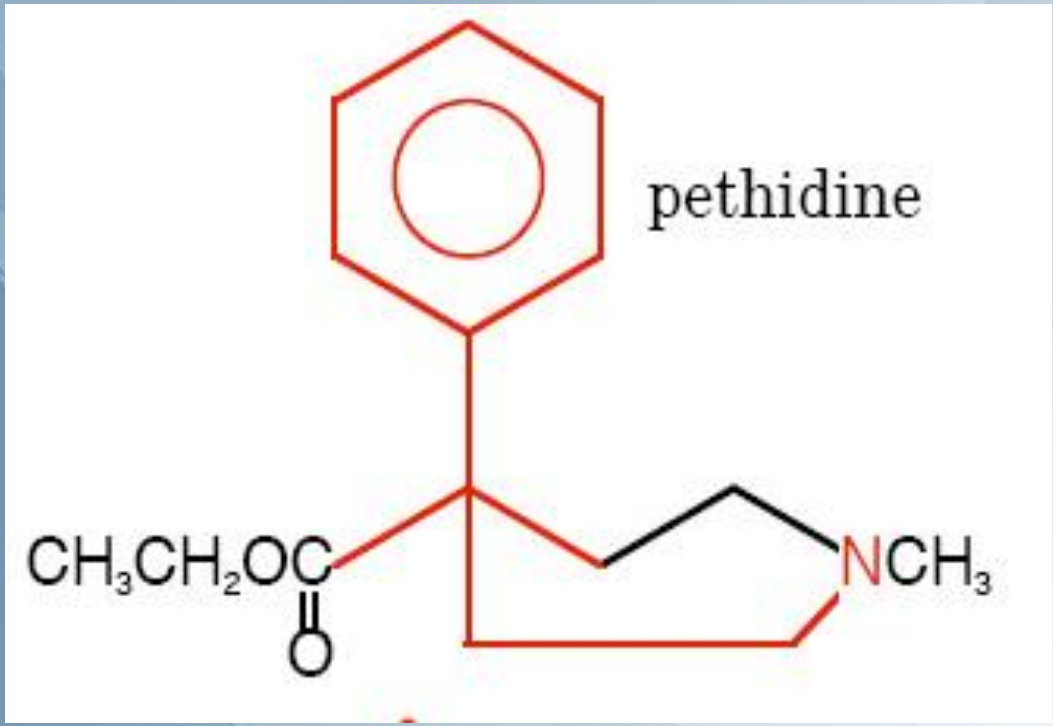
Makes “Meperidine”

Doesn't have any properties of atropine :-(

Dr W O Schumann
What does it actually do?
(working for IG Farben)



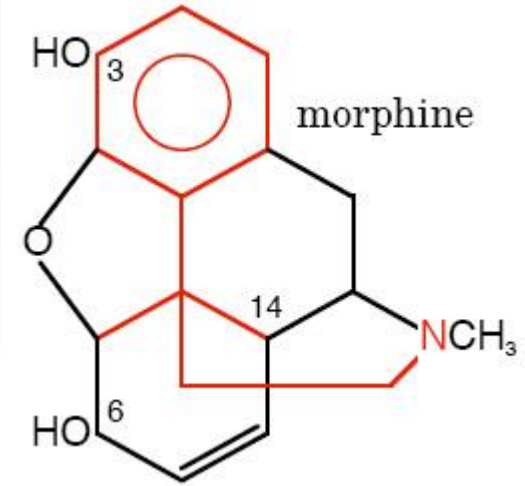
History and Pharmacology of LDN



- Meperidine turned out to be a very potent AGONIST of the opiate receptor (more potent than morphine).
- Renamed Pethidine
- Still used today

Structural similarities to Morphine – but different effects, and synthetic!

Serendipity – in trying to solve one problem, they solved another by accident.



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Big pharma goldrush

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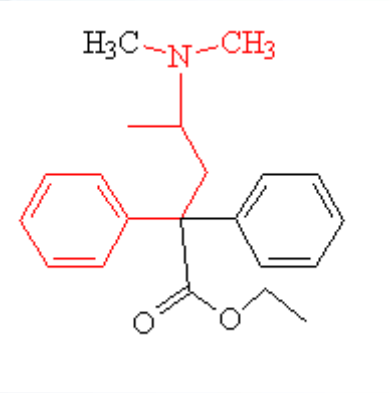

- 1940-46
- 1,1-diphenyl-1 (dimethylaminoisopropyl butanone-2

Methadone

- 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) Desmethylprodine
- N-allylnormorphine - Weijlard and Erikson (Merck & co) → unusual properties. (nalorphine)

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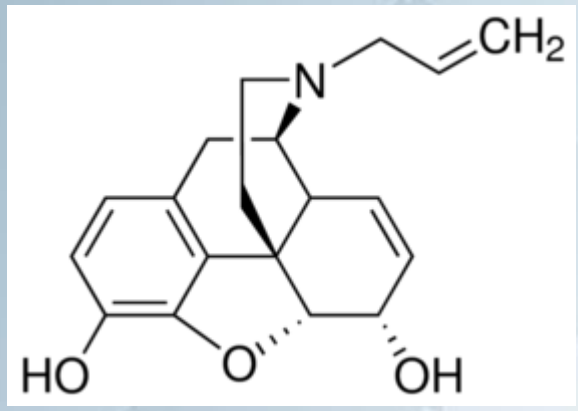

Nalorphine

Slight analgesic action in animals

Some effects attributable to morphine effects

Given to an animal overdosed with morphine it **reversed** the effects!

Realisation that this is USEFUL

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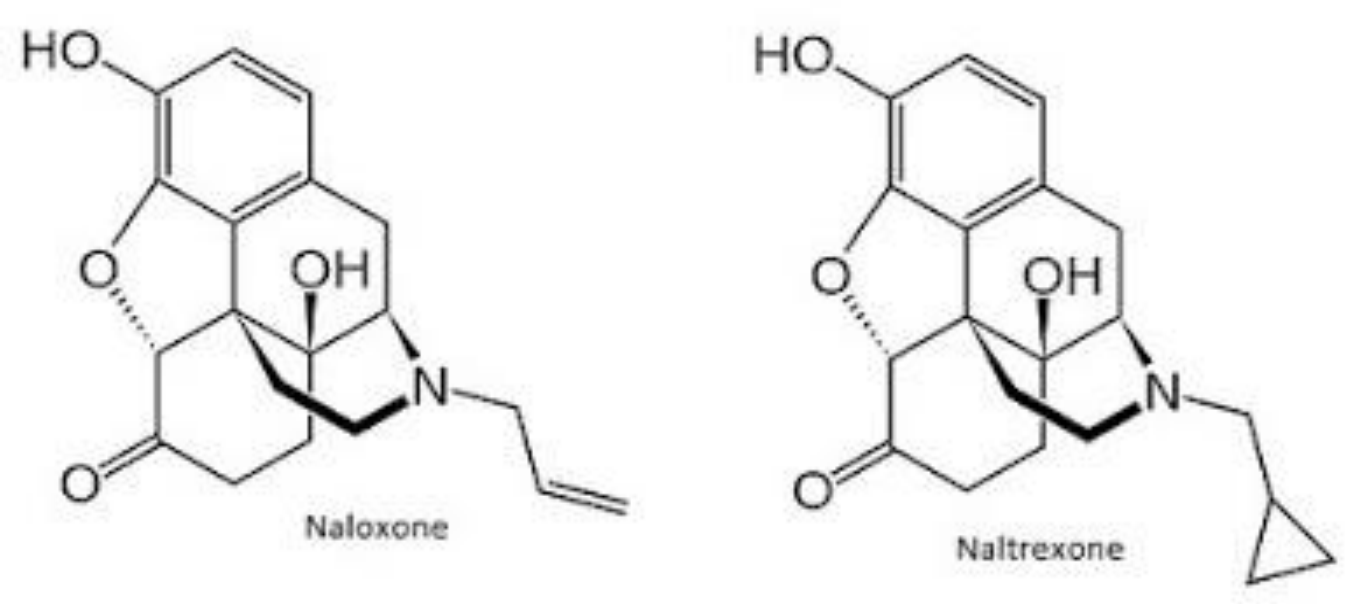

First patent for opiate blocking drug was for Naloxone in 1966.

WHO list of essential medicines – still there 50 years later

Its orally more active analog Naltrexone shown on the right.

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Don't
KEEP CALM

It's time to
WAKE UP

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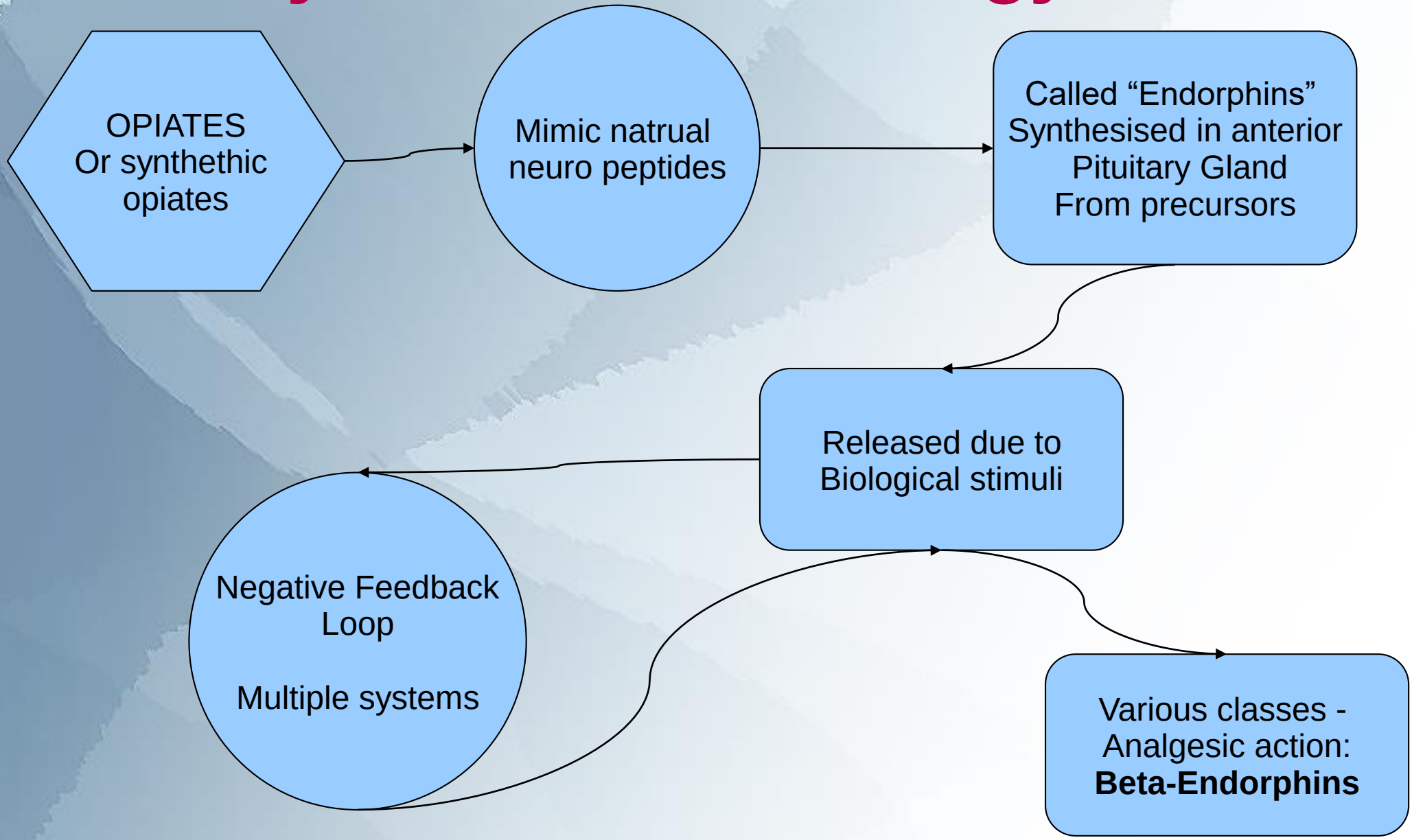

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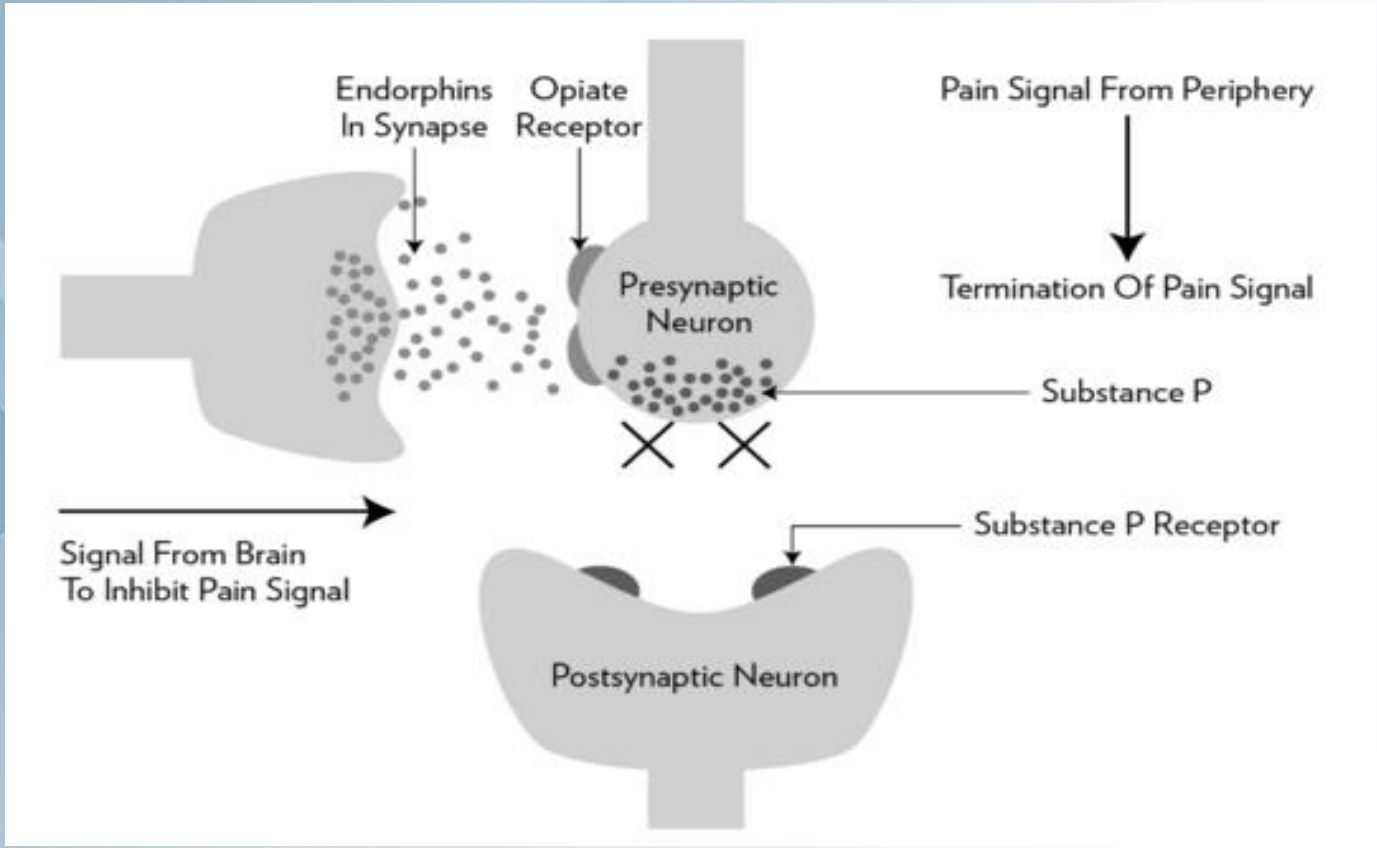
BETA Endorphins in the peripheral nervous system

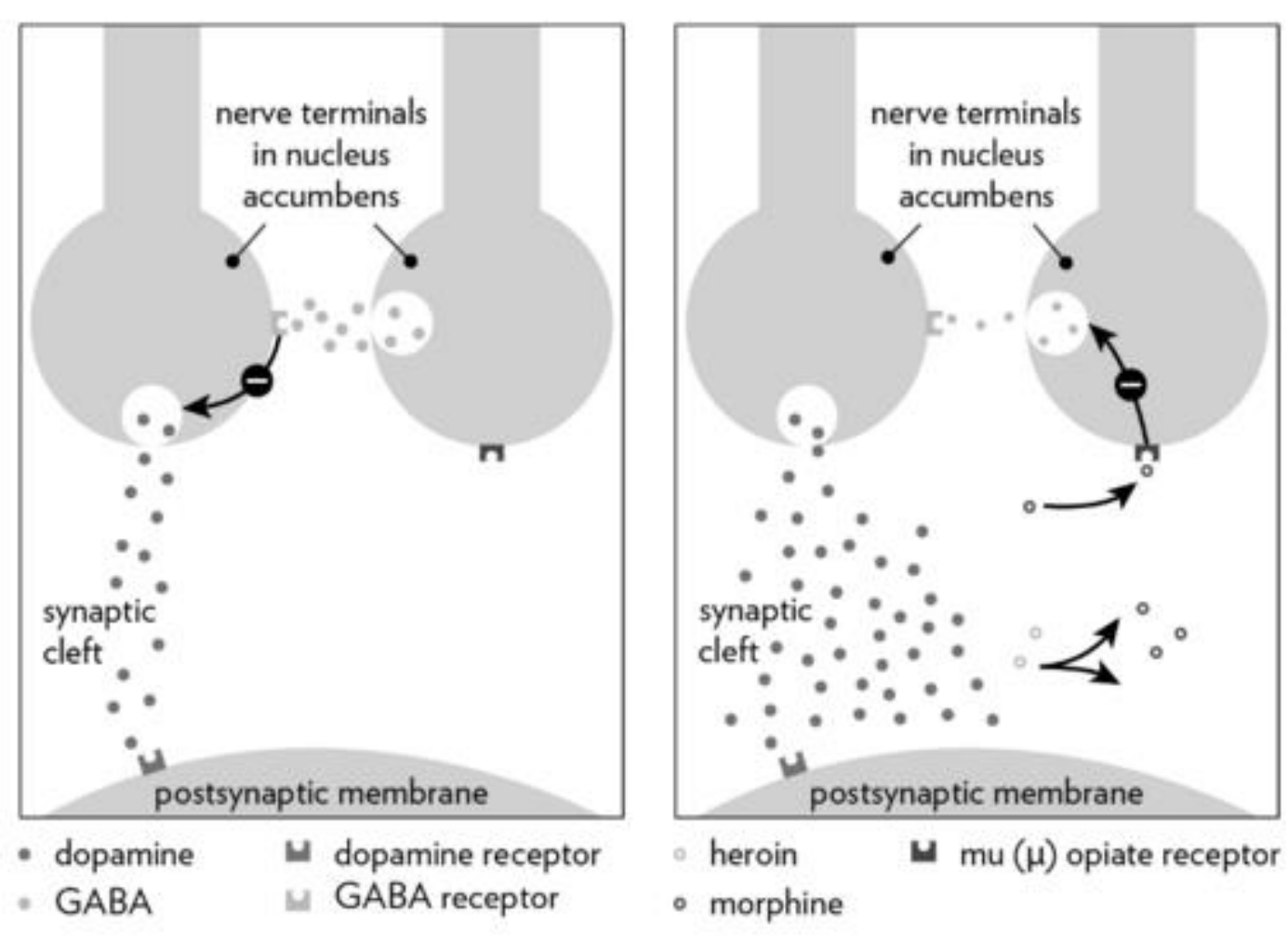


Range of neurotransmitters in addition to Substance P. Different opiate receptors. Mu is most common in this pathway.

History and Pharmacology of LDN

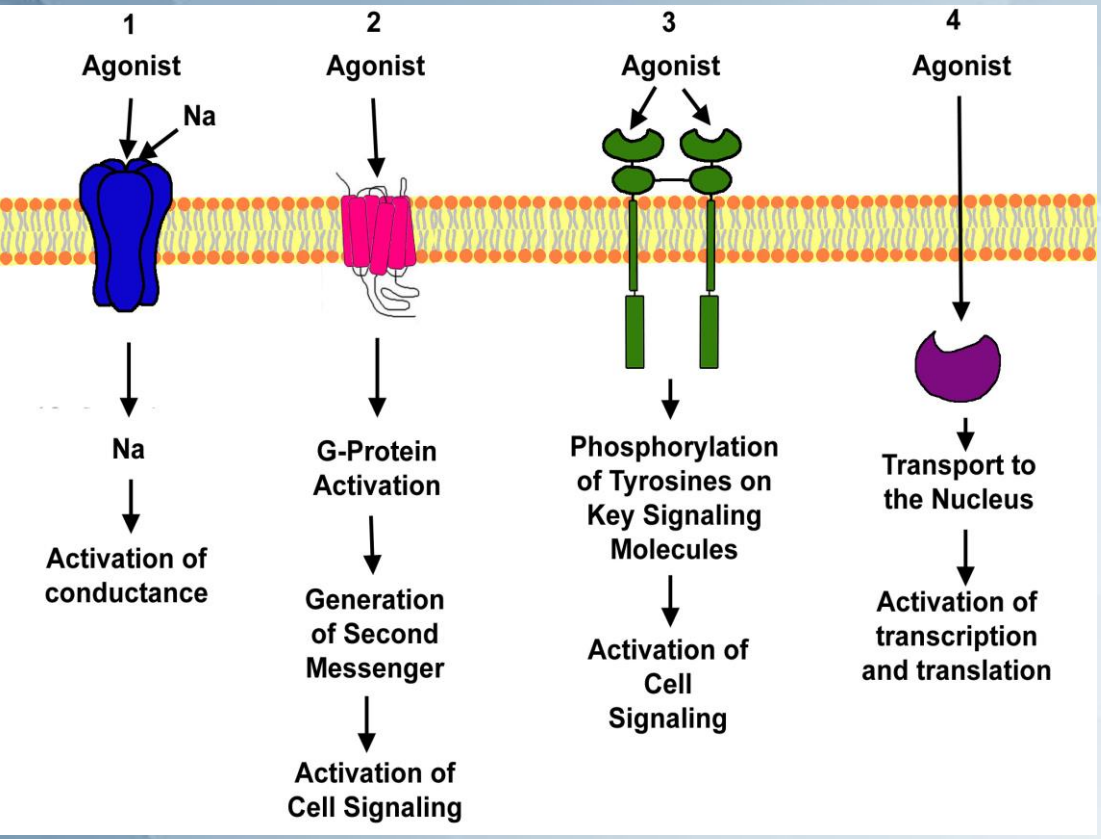
BETA Endorphins in the central nervous system

Dopamine!



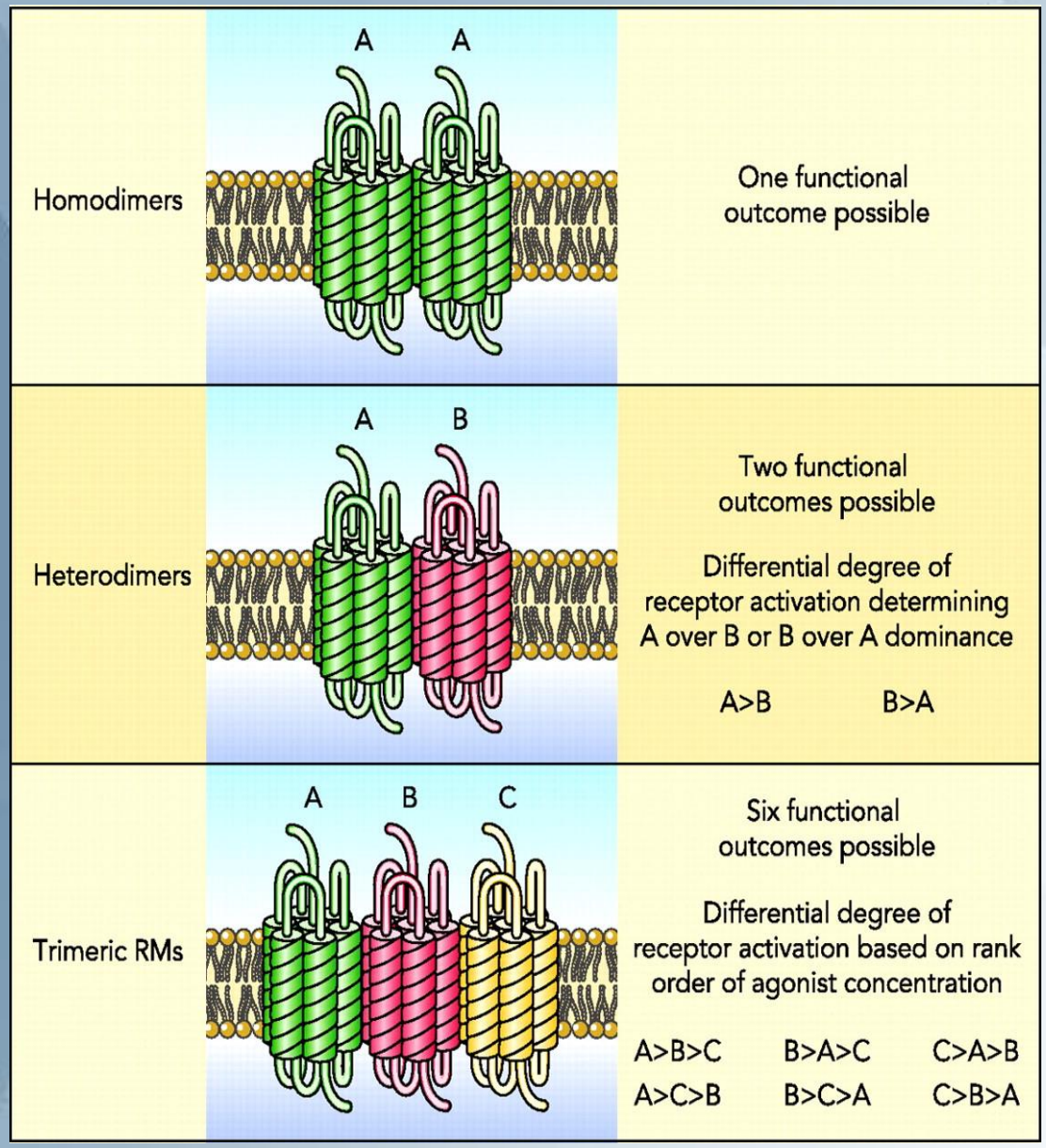
History and Pharmacology of LDN

Receptors



- Theorised in 1960s
- Discovered in 1970s, via radioisotope labelling.
- Opiate receptors are in a family of similar receptors – GProtein Activated
- Four broad groups now known

History and Pharmacology of LDN



G-Protein Family

Opiates

Somatostatin

TLR

Glucagon

Beta-Adrenergic

Etc (generally inhibitory when activated)

Multitude of outcomes

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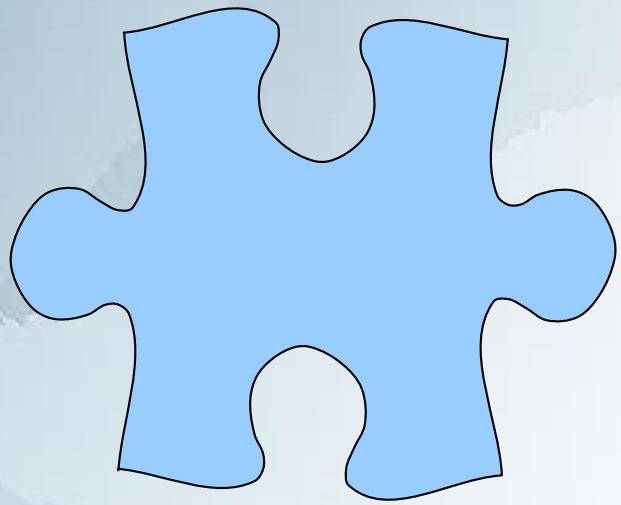
Opiate receptors in specific



AGONIST
Fits and
Activates
(Variable)

Partial agonist
-fits but doesnt
fully activate

Antagonist
Blocks

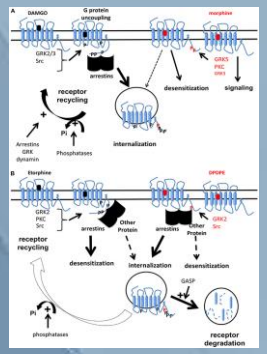
History and Pharmacology of LDN

Recap

Endogenous endorphins, such as the beta endorphin discussed earlier, are agonists;: these are mimicked by opiate drugs such as morphine and diamorphine. Naltrexone and naloxone are antagonists; keys which that fit the same door, but stop the receptor from being activated by an agonist. It has since been discovered that these receptors are fluid and can become more or less sensitive to agonists and can increase and decrease in active number depending on circumstances.

Extract from The LDN Book
Chapter 1

History and Pharmacology of LDN



Not supposed to be able to read this picture! It explains opiate receptor downregulation.

Simple version:

Analgesia

Euphoria

Regular Exposure to excess exogenous opiates

Reduced Sensitivity to All Opiates (inc End)

Receptors deactivate Or “internalise”

Natural Endogenous opiates

Naltrexone Blocks

Pharmacological addiction

History and Pharmacology of LDN

Use of naltrexone as therapy for addiction

50-300mg daily Licensed

Very successful – blocked all euphoric effects of heroin etc.

Short acting, so compliance often poor

Blocked natural endorphins, lead to dysphoria in some patients.

Recent resurgence in opiate antagonists for alcoholism Licensed

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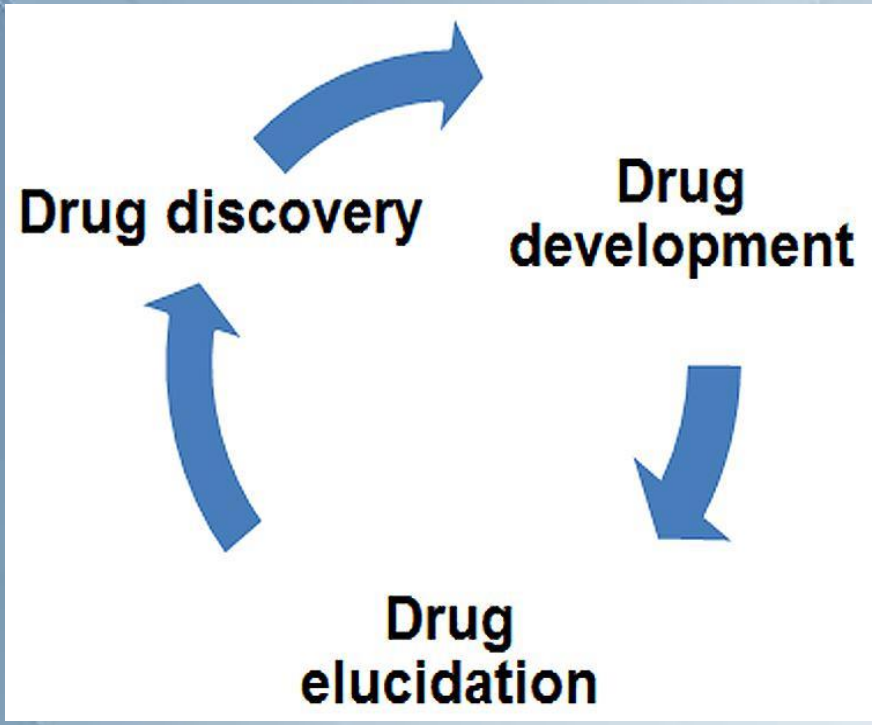
Naltrexone Immunological effects



Drugs are rarely 100% selective

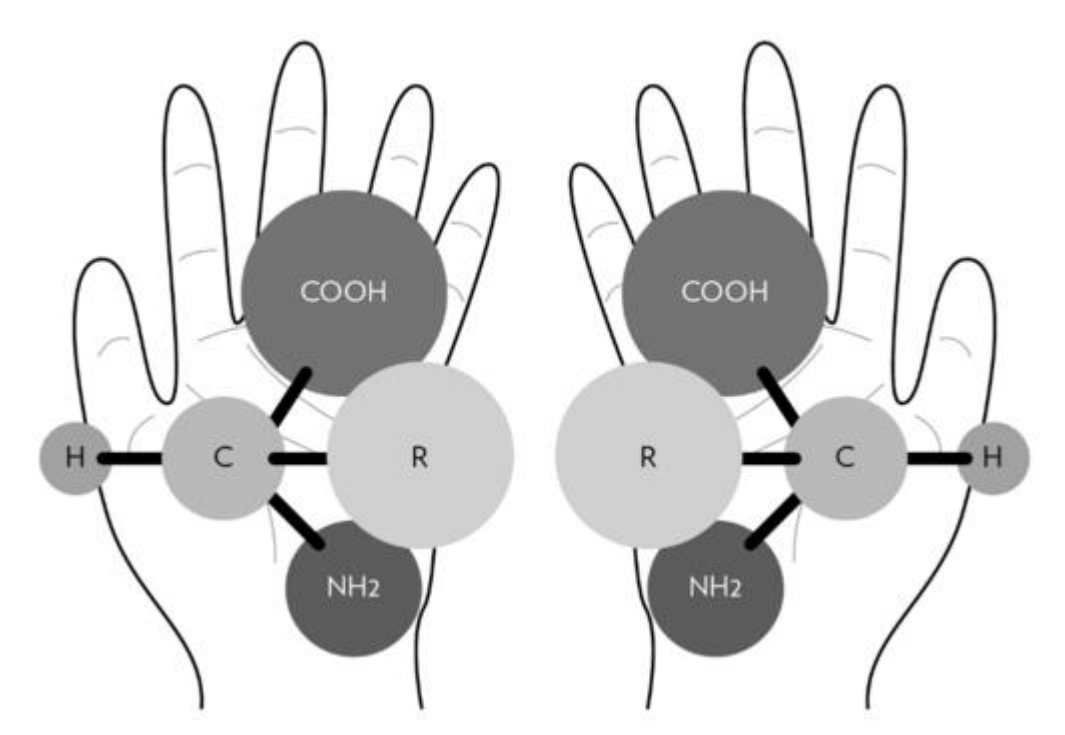
Often after launch, drugs undergo an elucidation period where previously unknown effects are found.

Science often improves – which assists this process.

Drugs which affect homeostasis can have different results in higher and lower doses

History and Pharmacology of LDN

Naltrexone Immunological effects



Drugs are three dimensional. (Chiral)

Usually synthesised in 50:50 raecemic mixture of L and R isomers.

Different ISOMERS can have different pharmacological targets

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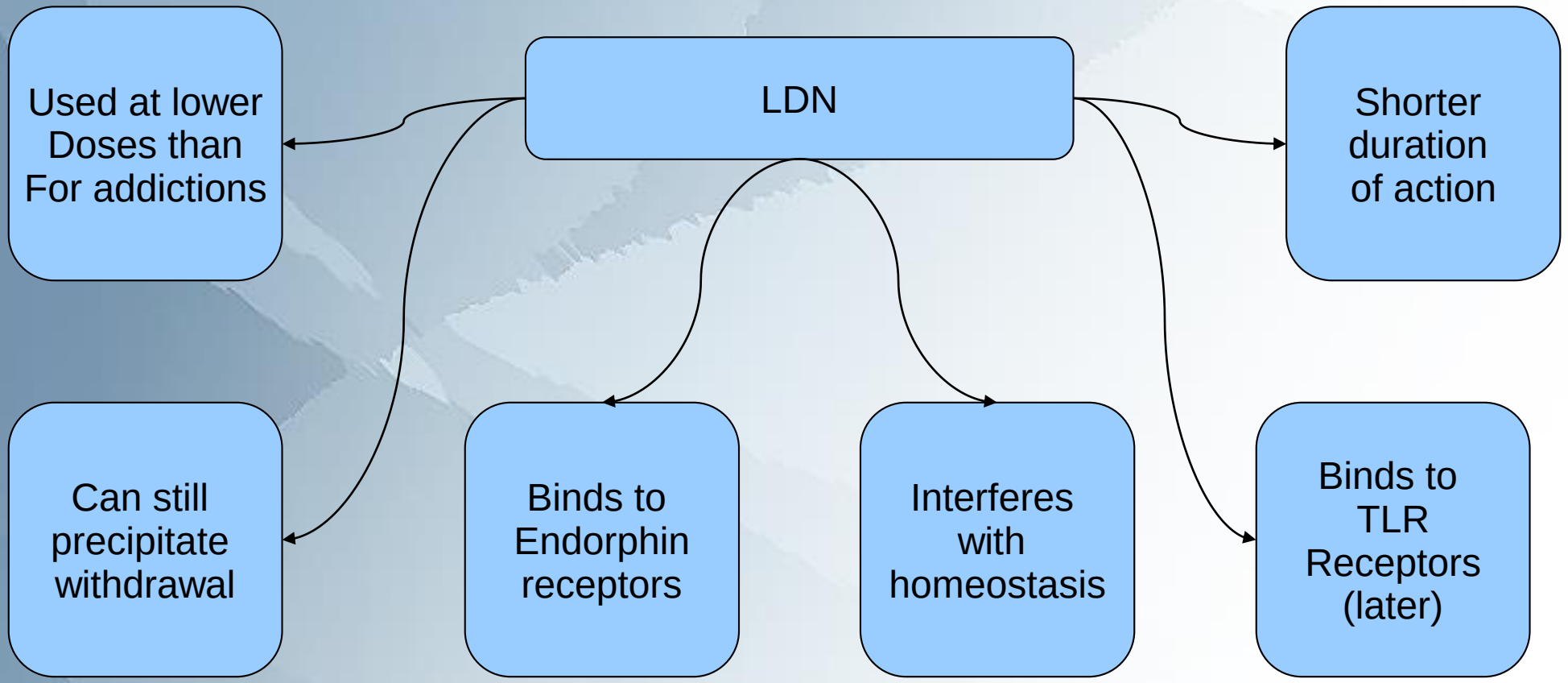
Naltrexone Immunological effects



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Naltrexone Immunological effects

1986 –> now Dr Ian Zagon

Endorphin receptors are present on vast array of immune cells

Endorphin receptors are coded in the mRNA of immune cells, important in regulating the biological response to infection and mutagens.

~30 years of research and ~300 papers the science is irrefutable

History and Pharmacology of LDN

Naltrexone Immunological effects

Zagon research summary

Many outward diseases
Are expressions of
Malfunctioning immune
system

Blocking opiate receptors briefly
using naltrexone causes an
up-regulation in the production
of endorphins, which can act
in an immunomodulatory way
to correct immune
system malfunction

The immune system
is regulated by
Endorphins
- acting primarily on
Opiate receptors

Cell proliferation is mediated by a subtype of endorphins.
Important in cancer?

History and Pharmacology of LDN

Naltrexone Immunological effects

Experimental Models

- Wound Healing
- MS
- Ocular surface disease
- Chrohn's Disease
- Pancreatic Cancer
- Breast Cancer

Ridiculous simplification

This list grows constantly and is not exhaustive...

History and Pharmacology of LDN

Naltrexone Immunological effects

Toll Like Receptors

Demonstrated first in 1985 by Christiane Nüsslein-Volhard.

Present on immune cells all over the body, macrophages, dendritic cells, neutrophils, b-lymphocytes, mast cells, monocytes, and on various internal organs.

First line defense against invasion from bacteria and other pathogens

Can produce NF-Kappa-B as part of the signaling mechanism.

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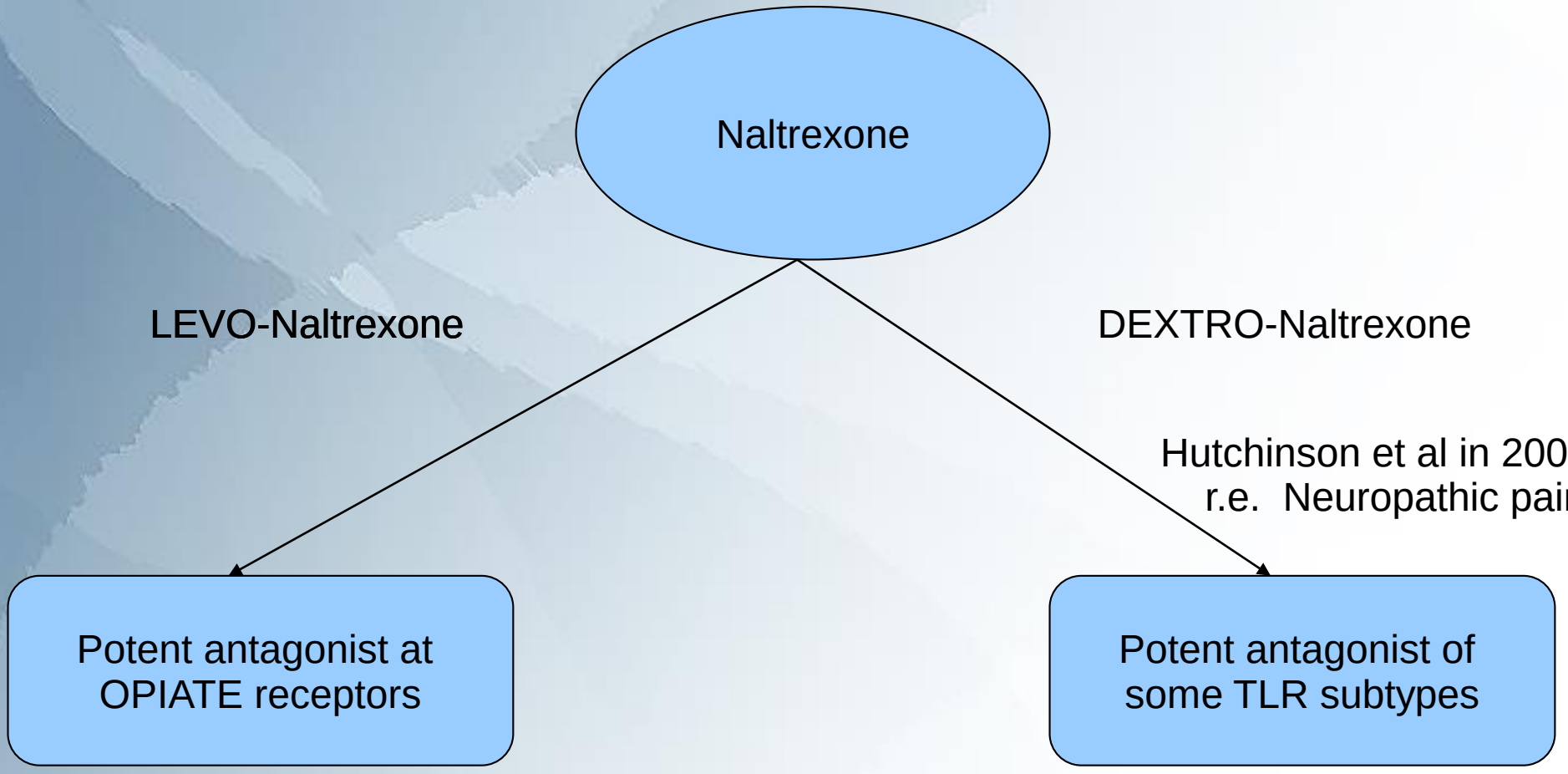
Naltrexone Immunological effects

Toll Like Receptors



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Naltrexone Effects Summary