

獸醫藥理學概論

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課程大綱

- ❖ 認識動物用藥品
- ❖ 獸醫藥理學課程單元
 - ❧ Pimobendan、sildenafil (Viagra®)
- ❖ 獸醫藥理學之特點
 - ❧ 藥物動力學之特點
 - ❧ 中樞神經系統藥理之特點
 - ❧ 內分泌藥理之特點

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聲明事項

本講義僅供參與『113年動物用藥品販賣業藥品管理技術人員訓練』學員之個人學習之教育訓練用途，不作任何其他用途。學員不得截圖、轉發、轉載、發布本講義之任何一部分至他人或任何平台。

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重點提醒

- ❖ 威而鋼：作用機轉&獸醫學用途
- ❖ Ion trapping: urine pH & 藥物的排除
- ❖ Alpha-2 agonists: xylazine abuse; oromucosal dexmedetomidine dog
- ❖ Etorphine: 10000x morphine, 大型動物
- ❖ Ketamine: NMDA; IM
- ❖ Diazepam used in cats
- ❖ 同化性類固醇藥物：
 - ⌘ Stanozolol、boldenone改善動物衰弱的體質
 - ⌘ Trenbolone生長促進劑

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❖認識動物用藥品

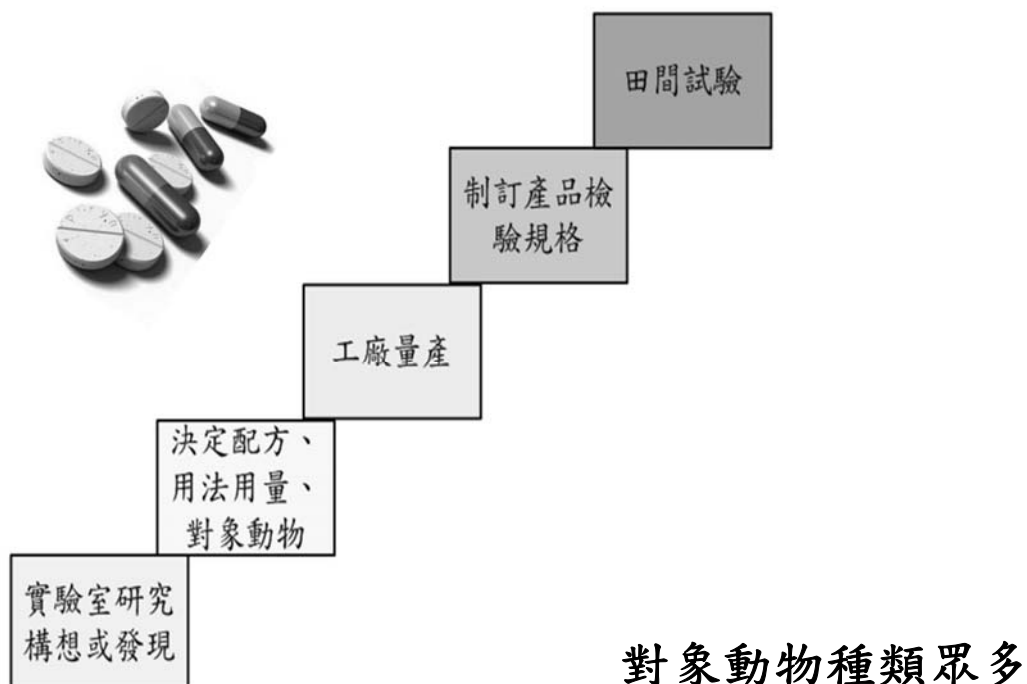
❧動物用藥品檢驗登記

❧寵物用藥簡介

❧產食動物用藥簡介

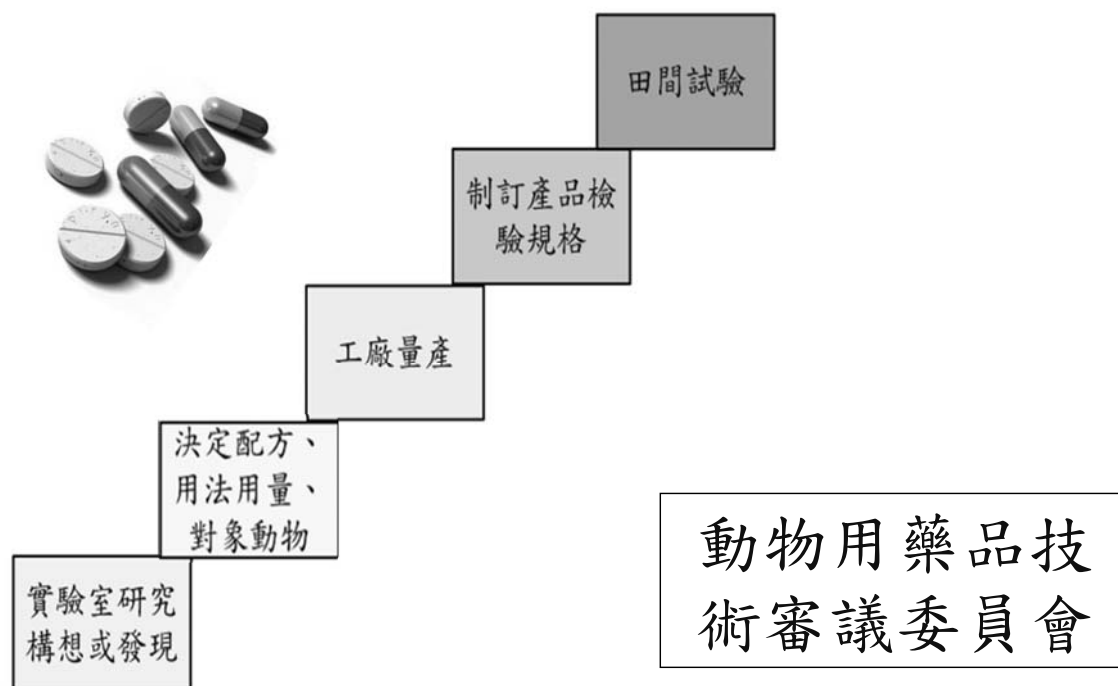
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動物用藥品新藥研發上市



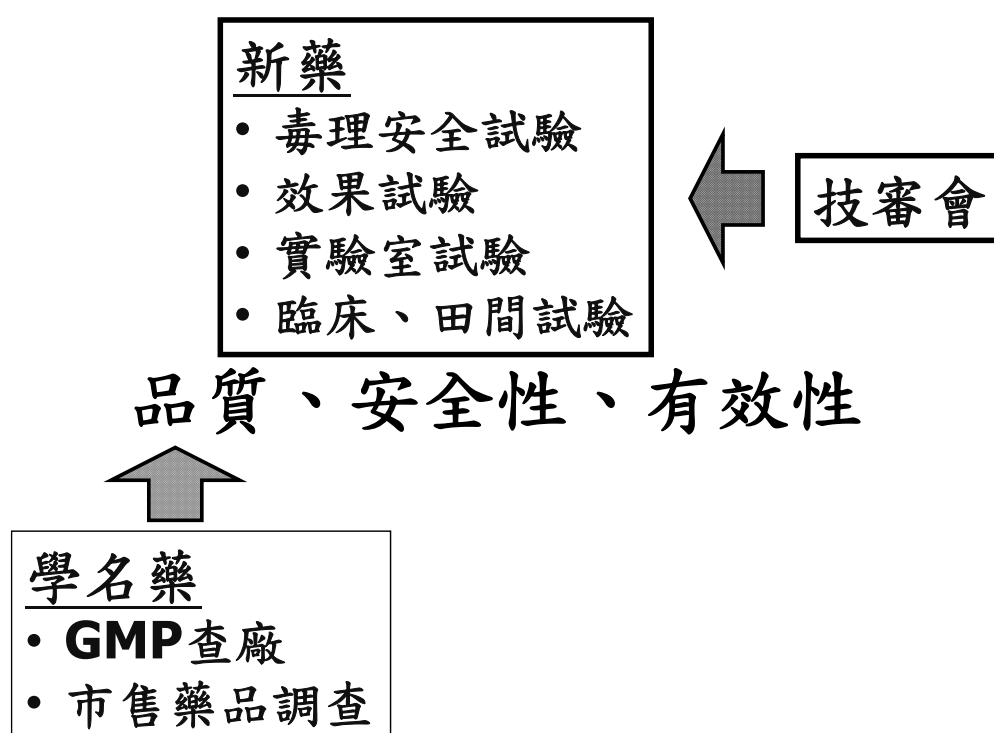
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動物用藥品新藥檢驗登記



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藥品的三大元素



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法規

❖ 母法：動物用藥品管理法

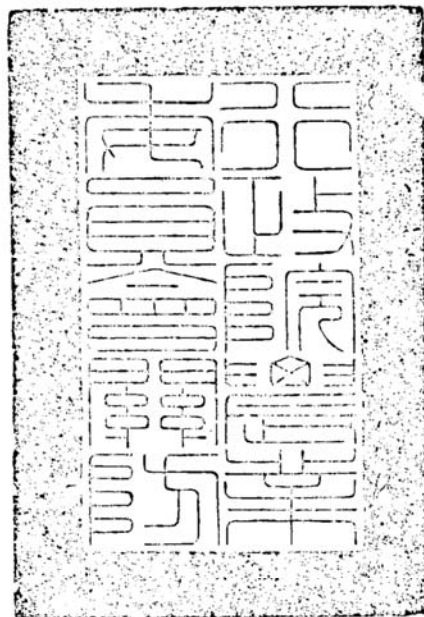
❖ 檢驗登記規定於第12條：

- ❧ 製造或輸入動物用藥品，應將其成分、性能、製法之要旨、分析方法及有關資料或證件，連同標籤、仿單及樣品，並繳納證書費、檢驗費，申請中央主管機關檢驗登記，經核准發給許可證後，始得製造或輸入
- ❧ 前項動物用藥品檢驗登記、審查程序、許可證之變更、展延、補發、換發、廢止及其他應遵行事項之準則，由中央主管機關定之

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行政院農業委員會 令

發文日期：中華民國104年03月13日
發文字號：農防字第1041471377號



訂定「動物用藥品檢驗登記審查準則」。
附「動物用藥品檢驗登記審查準則」

主任委員 陳保基

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附件明確規定應檢附之資料

附件	
1	動物用藥品送驗應檢附之樣品及資料
2	一般藥品學名藥&原料藥
3	生物藥品
4	消毒藥品
5	一般藥品新藥，含基本資料及技術資料
6	專供輸出

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動物用藥品新藥檢驗登記

新藥類別	背景資料	藥物動力學	毒理安全性		殘留試驗		效果試驗	安定性
			實驗動物	對象動物	實驗動物代謝	對象動物殘留		
新成分	○	○	○	○	○	○	○	○
鹽類不同之新成分	○	○a	○a	○a	○	○	○a	○
新複方	○	○	○b	○	○	○	○	○
新劑型	○	○	×	○a	×	○	○a	○
新單位含量 (包括不同濃度製劑)	○	×	×	○a	×	○	○a	○
新投藥途徑	○	×	×	○	×	○	○a	×
新劑量	○	×	×	×	×	○	○	×
新療效	○	×	×	×	×	×	○	×
新對象動物	○	×	×	○	×	○	○	×

○及×：表示必須及不必檢附該項目之資料

a：表示可用“生物相等性”資料代替

b：係指包括急性、亞急性及致突變性試驗資料

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動物用藥品vs.人用藥品

- ❖ 法規：動物用藥品管理法、藥事法
- ❖ 主管機關：農業部動植物防疫檢疫署、衛生福利部食品藥物管理署
- ❖ 對象：動物、人
 - ⊕ 伴侶動物(寵物)：犬貓兔鼠龜…
 - ⊕ 經濟動物：豬雞牛羊鴨鵝魚鰲蝦…
 - ⊕ 其他：馬鴿子蜥蜴、動物園等
- ❖ 處方：獸醫師、醫師
- ❖ 調劑：獸醫師、藥師

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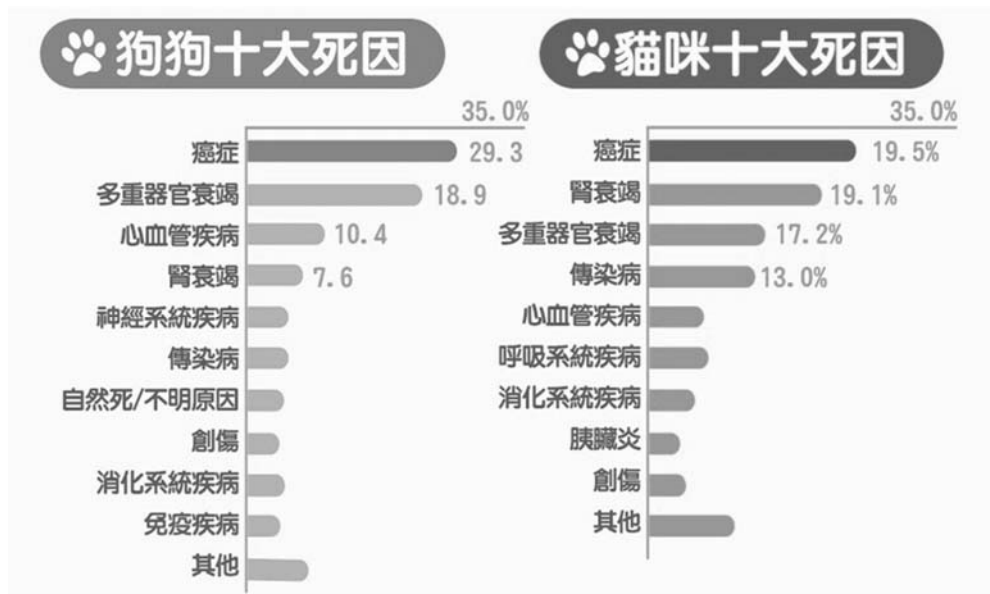
動物保健產業趨勢



<https://i2.wp.com/www.trendsightinc.com/wp-content/uploads/2018/12/%E6%93%B7%E5%8F%961.jpg>

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寵物(犬貓為主)用藥和人類相似
人用藥品約70%，動物用藥僅30%



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寵物用藥之特性(1)

- ❖ 疫苗接種
- ❖ 寄生蟲防治
 - ☞ 腸道寄生蟲：蛔蟲、鉤蟲、鞭蟲等
 - ☞ 心絲蟲(*Dirofilaria immitis*)：寄生在心臟的一種絲狀寄生蟲
 - ☞ 外寄生蟲：跳蚤、壁蝨……
- ❖ 寵物高齡化相關疾病：癌症化學治療、退化性關節炎、心臟衰竭、腎衰竭…
- ❖ 過敏性疾病：異位性皮膚炎、氣喘…

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寵物用藥之特性(2)

- ❖ 外科手術
- ❖ 影像學檢查: X光、電腦斷層、MRI...
- ❖ 高度依賴麻醉劑
 - ☞ 吸入性麻醉劑(氣體、揮發性液體)
 - ☞ 注射用麻醉劑
- ❖ 麻醉保定
 - ☞ 精神安定藥物: 鎮靜劑、寧神劑...
 - ☞ 疼痛控制: 類鴉片止痛劑...
- ❖ 影響動物行為用藥: 焦慮&壓力問題

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產食動物用藥

動物用藥品對禽畜養殖的效用

- ◆ 疫苗: 預防畜禽動物疾病, 避免疫情擴大
 - 病毒性疾病的控制以疫苗為主'
- ◆ 抗菌劑、寄生蟲防治: 主要仰賴化學藥劑
- ◆ 促進生長, 改進飼料效率, 提高生產力
- ◆ 飼料添加抗菌劑、受體素(瘦肉精)
- ◆ 內分泌藥理(荷爾蒙)

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獸醫藥理學課程單元

❖ 總論

- ❧ 藥物吸收、分布及作用原理
- ❧ 藥效學Pharmacodynamics
- ❧ 藥物動力學Pharmacokinetics

❖ 食品安全性：產食動物的組織殘留

❖ 系統藥理Systemic pharmacology

❖ 化學治療Chemotherapy

- ❧ 抗細菌、黴菌、病毒、寄生蟲、腫瘤用藥

❖ 藥物交互作用&藥物不良反應



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系統藥理Systemic Pharmacology

❖ 神經系統藥物

- ❧ 自主神經系統藥物

❖ 交感、副交感神經藥物、骨骼肌鬆弛劑

- ❧ 中樞神經系統藥物

❖ 麻醉劑、局部麻醉劑、止痛劑、鎮靜寧神劑、抗痙攣劑、中樞興奮劑

- ❧ 影響動物行為的藥物

❖ 抗焦慮劑、抗憂鬱劑

- ❧ 中樞神經系統藥理之特點

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中樞神經系統藥理之特點

- ❖ α_2 -agonist tranquilizers
 - ⌘ Human drug: anti-hypertensive
 - ⌘ Animal drug: pre-anesthetic medication, chemical restrain, anxiety
- ❖ Dissociative anesthetics
- ❖ Opioids for wild animals
- ❖ Antidepressants
 - ⌘ Human: major depression
 - ⌘ Animal: behavioral modification

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Systemic Pharmacology

- ❖ 心血管藥理
 - ⌘ 心衰竭治療藥物
 - ⌘ 抗心律不整藥物 **Antiarrhythmic drugs**
 - ⌘ 血管擴張劑
 - ⌘ 鈣離子通道阻斷劑
 - ⌘ 處理血栓疾病之藥物
 - ❖ 抗凝劑：heparin
 - ❖ 口服抗凝劑：warfarin
 - ❖ 抗血小板藥物：NSAID (i.e., aspirin)

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Systemic Pharmacology

❖ 呼吸系統藥理

↻ 氣喘治療藥物 **Anti-asthmatics**

❖ 支氣管擴張劑 **Broncodilators**

❖ 抗發炎藥物 **anti-inflammatory drugs**

↻ 止咳劑 **Anti-tussives**

↻ 化痰劑 **Mucolytics**

↻ 祛痰劑 **Expectorants**

↻ 肺高壓 **pulmonary hypertension** 治療藥物

❖ **Sildenafil (Viagra® 威而鋼)**

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Canine Pulmonary Hypertension 犬肺動脈高血壓

❖ **Treatment of underlying causes is important**

❖ **Sildenafil (Viagra®, Pfizer), vardenafil (GlaxoSmithKline) & tadalafil (Eli Lilly)**

↻ **Phosphodiesterase (PDE) type V inhibitors**

↻ **↑ cGMP levels in vascular smooth muscle cells**

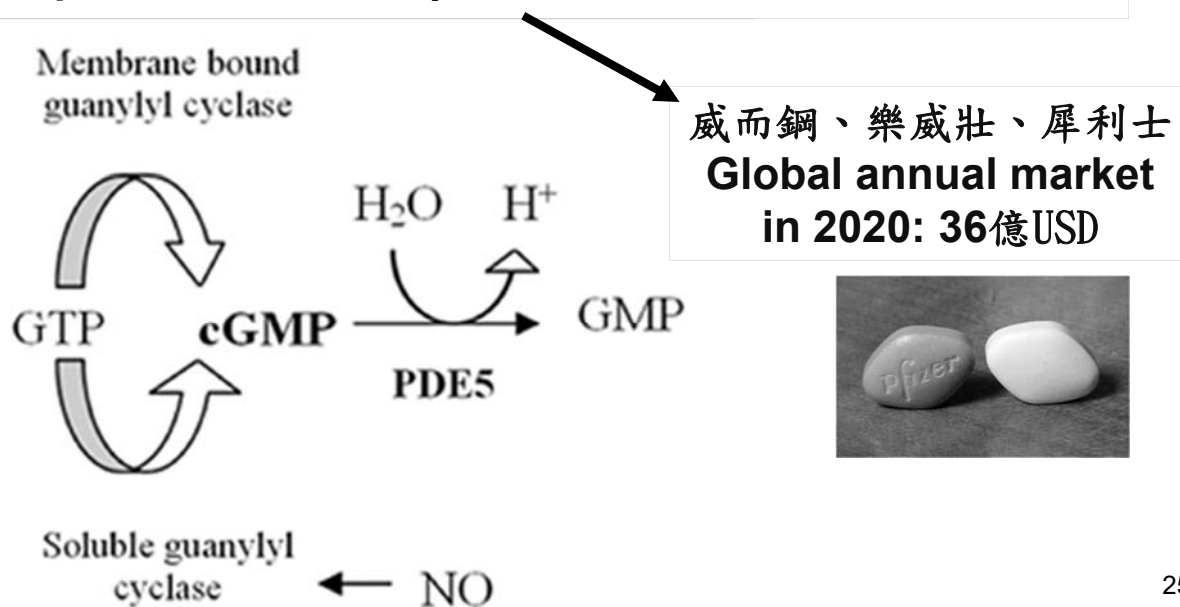
↻ **Induces vasodilation & reduces pulmonary hypertension in dogs & humans**

↻ **Side effects: hypotension**

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Phosphodiesterase V

- ❖ Found in brain, lung, heart, liver, kidneys, bladder, prostate, urethra, penis, uterus & skeletal muscles



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High Altitude Illness 高海拔疾病

- ❖ Cerebral edema due to cerebral vasodilation
- ❖ Pulmonary hypertension and edema due to vasoconstriction
- ❖ Sildenafil (Viagra®), tadalafil, vardenafil: vasodilation
- ❖ Acetazolamide (diuretic drug): slight metabolic acidosis (bicarbonate excretion) that stimulates respiratory center
- ❖ Nifedipine: Ca^{++} channel blocker, vasodilation
- ❖ Dexamethasone: relieve edema symptoms, mechanisms unknown

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Systemic Pharmacology

❖ 消化系統藥理

☞ 潰瘍治療藥物

❖ 胃液分泌抑制劑

❖ 黏膜保護劑

☞ 促動劑

☞ 催吐劑、止吐劑

☞ 瀉劑、止瀉劑

☞ 炎症性腸道疾病治療藥物

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Systemic Pharmacology

❖ 內分泌藥理

☞ 腦下垂體

☞ 甲狀腺

☞ 胰臟

☞ 腎上腺

❖ 類固醇藥物 **Glucocorticoids**；重要的抗發炎藥物，用於氣喘、過敏性疾病、脊髓損傷等

☞ 生殖系統

❖ 同化作用賀爾蒙應用於畜產養殖

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化學治療Chemotherapy

❖ 抗微生物藥物

☞ 細菌、黴菌、病毒

❖ 抗腫瘤藥物

❖ 驅蟲藥

☞ 體內寄生蟲：心絲蟲、腸道寄生蟲

☞ 體外寄生蟲：跳蚤、壁蝨、蟎

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獸醫藥理學之特點

❖ 藥物動力學之特點

❖ 中樞神經系統藥理之特點

❖ 產食動物之內分泌藥理

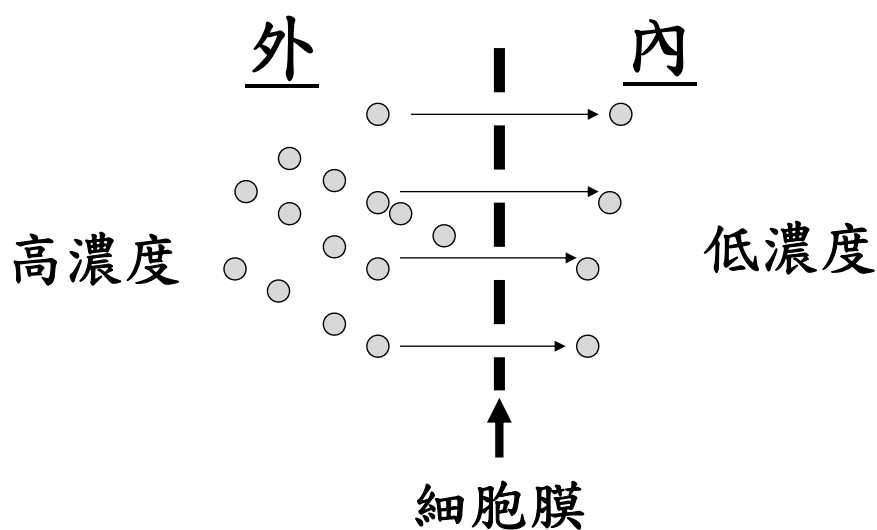
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藥物動力學之特點

- ❖ 藥物分布與pH的相關性
 - ∞ Ion trapping of drugs
 - ∞ pH partition theory
 - ∞ Antibiotics in cow milk
- ❖ 藥物代謝&毒性(NSAID)
 - ∞ Acetaminophen: cat toxicity
 - ∞ Diclofenac: vulture crisis

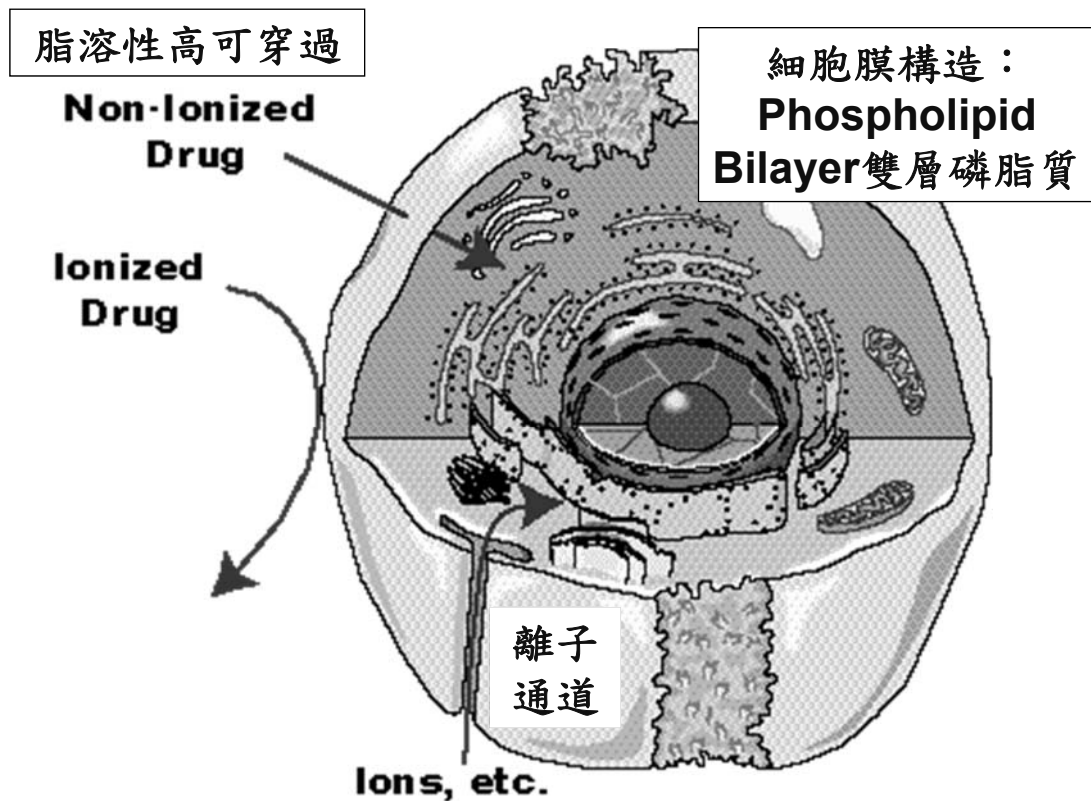
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被動擴散(Passive diffusion)



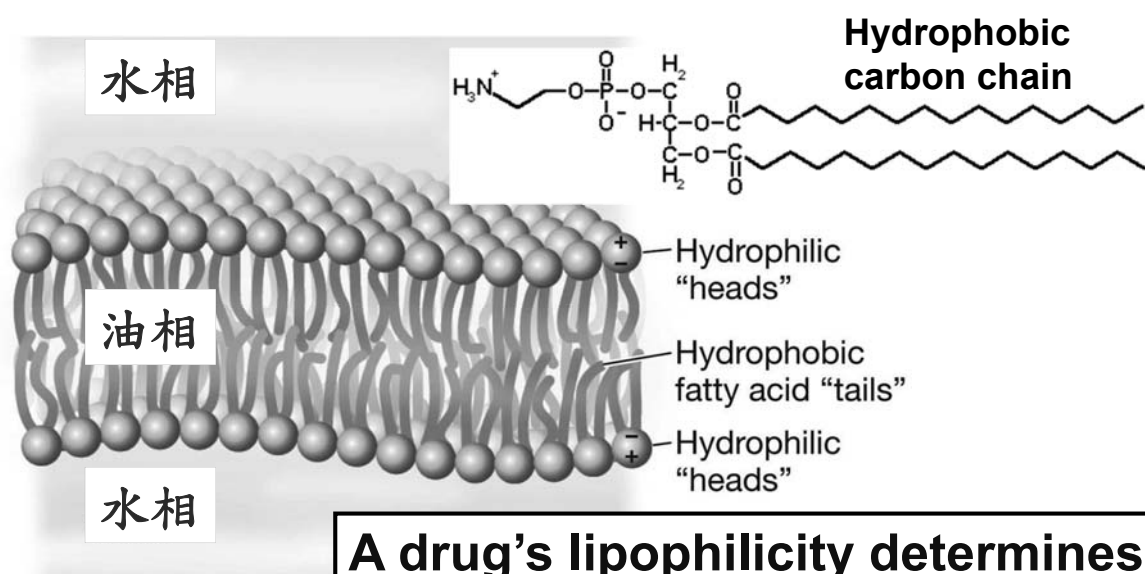
被動擴散是大多數藥物吸收進入體內以及在體內移動的方式

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Phospholipid Bilayer 雙層磷脂質



A drug's lipophilicity determines the rate of transmembrane movement (diffusion)

Fick's Law of Diffusion

(科學家Adolf Fick於1855提出)

$$\frac{dQ}{dt} = \left(\frac{DAK_p}{h} \right) (C_1 - C_2)$$

擴散速率 膜厚度 濃度差

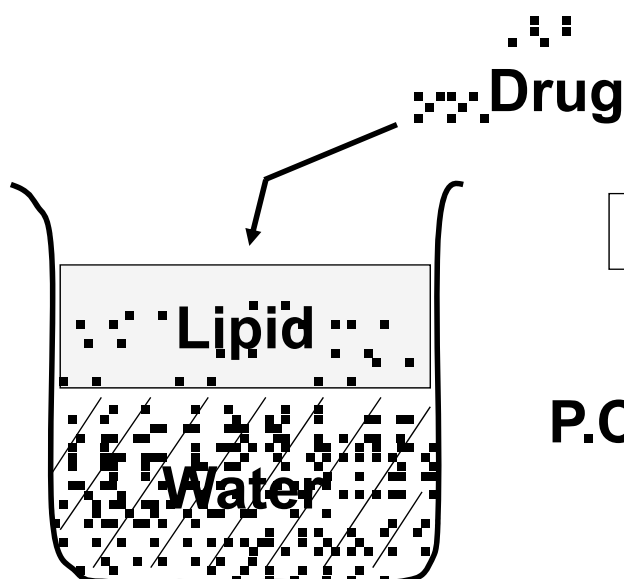
D：擴散係數，是一個常數

A：擴散的面積

Kp：油水分配係數 Why Kp?

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Lipid-Water Partition Coefficient (油-水分配係數)



Lipid → Octanol

$$P.C. = \frac{[Drug]_{lipid}}{[Drug]_{water}}$$

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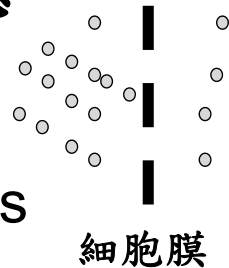
油-水分配係數

- The ratio of the concentration of the drug in two immiscible phases不相容油水兩相的比值：
 - A nonpolar liquid or organic solvent油相
(representing the membrane代表細胞膜)
 - An aqueous buffer水相
(representing the blood代表血液)
- The higher the lipid/water p.c. the greater the rate of transfer across the membrane
 - 油-水分配係數愈高，親脂性愈高，穿過細胞膜的速率愈快

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Ion Trapping離子捕捉效應

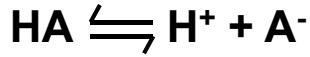
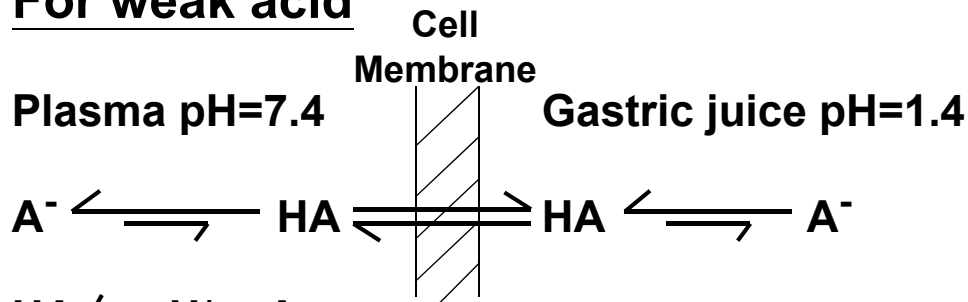
- Different amounts of total drug are found across cell membranes because of a **pH gradient**
 - More total drug is found on the side where ionization occurs to the greatest extent
- pH影響藥物的解離(ionization)程度
- 解離態(離子化)的藥物無法穿過細胞膜



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Handerson and Hasselbalch Equation

For weak acid



$$K_a = \frac{[A^-][H^+]}{[HA]}$$

$$[H^+] = k_a \frac{[HA]}{[A^-]}$$

$$-\log[H^+] = -\log k_a \frac{[HA]}{[A^-]}$$

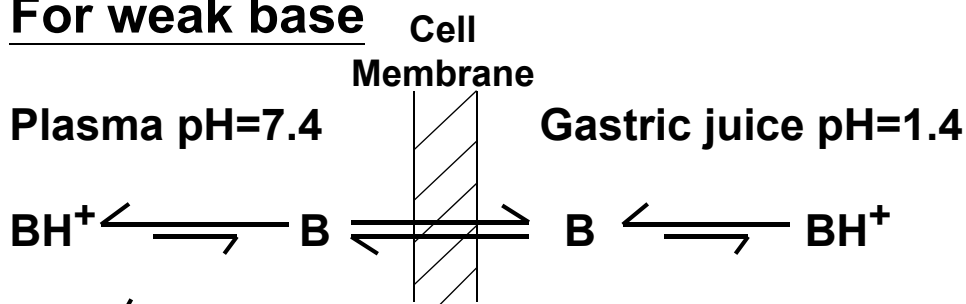
$$-\log[H^+] = -\log k_a + \log \frac{[A^-]}{[HA]}$$

$$pH = pka + \log \frac{[A^-]}{[HA]}$$

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Handerson and Hasselbalch equation

For weak base



$$K_b = \frac{[B^+][OH^-]}{[BOH]}$$

$$[OH^-] = k_b \frac{[BOH]}{[B^+]}$$

$$-\log[OH^-] = -\log k_b - \log \frac{[BOH]}{[B^+]}$$

$$pOH = pkb + \log \frac{[B^+]}{[BOH]}$$

$$pH = 14 - pOH = 14 - pkb - \log \frac{[B^+]}{[BOH]} = pka - \log \frac{[B^+]}{[BOH]}$$

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Learning Question

What is the percentage of ionized form of 阿斯匹林 aspirin ($pK_a = 3.4$) in plasma ($pH = 7.4$) ?

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

$$7.4 = 3.4 + \log \frac{[A^-]}{[HA]}$$

$$\log \frac{[A^-]}{[HA]} = 4 \quad \frac{[A^-]}{[HA]} = 10^4 = 10000$$

Therefore, 99.99% of aspirin is ionized form.

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弱酸性藥物在血液和胃液之間的分布比率

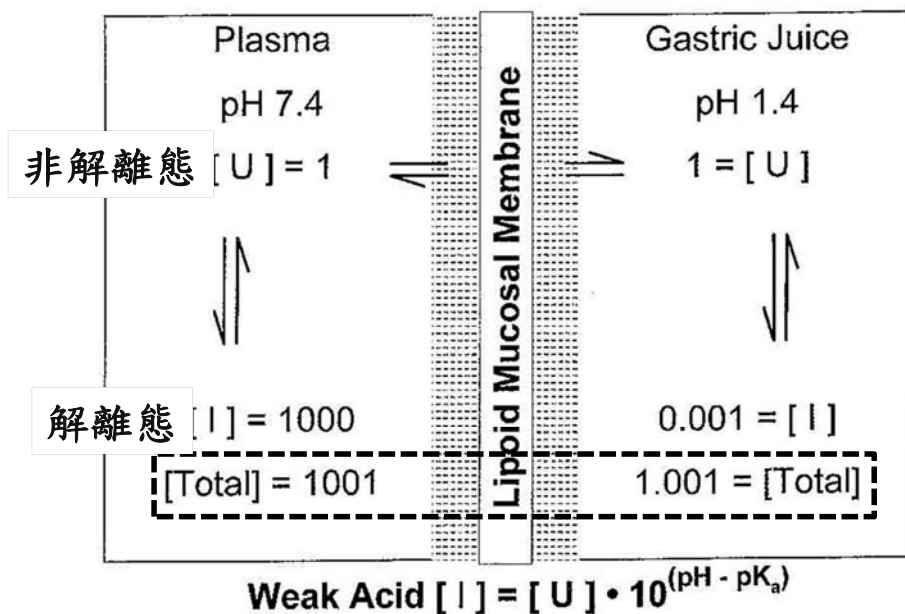


FIG. 3.2—Effect of pH gradient on distribution of a weak organic acid (pK_a 4.4) between blood plasma (pH 7.4) and gastric juice (pH 1.4). In this figure, $[I]$ and $[U]$ represent the concentrations of the ionized and nonionized fractions of the drug, respectively. A dynamic equilibrium exists between ionized and nonionized drug.

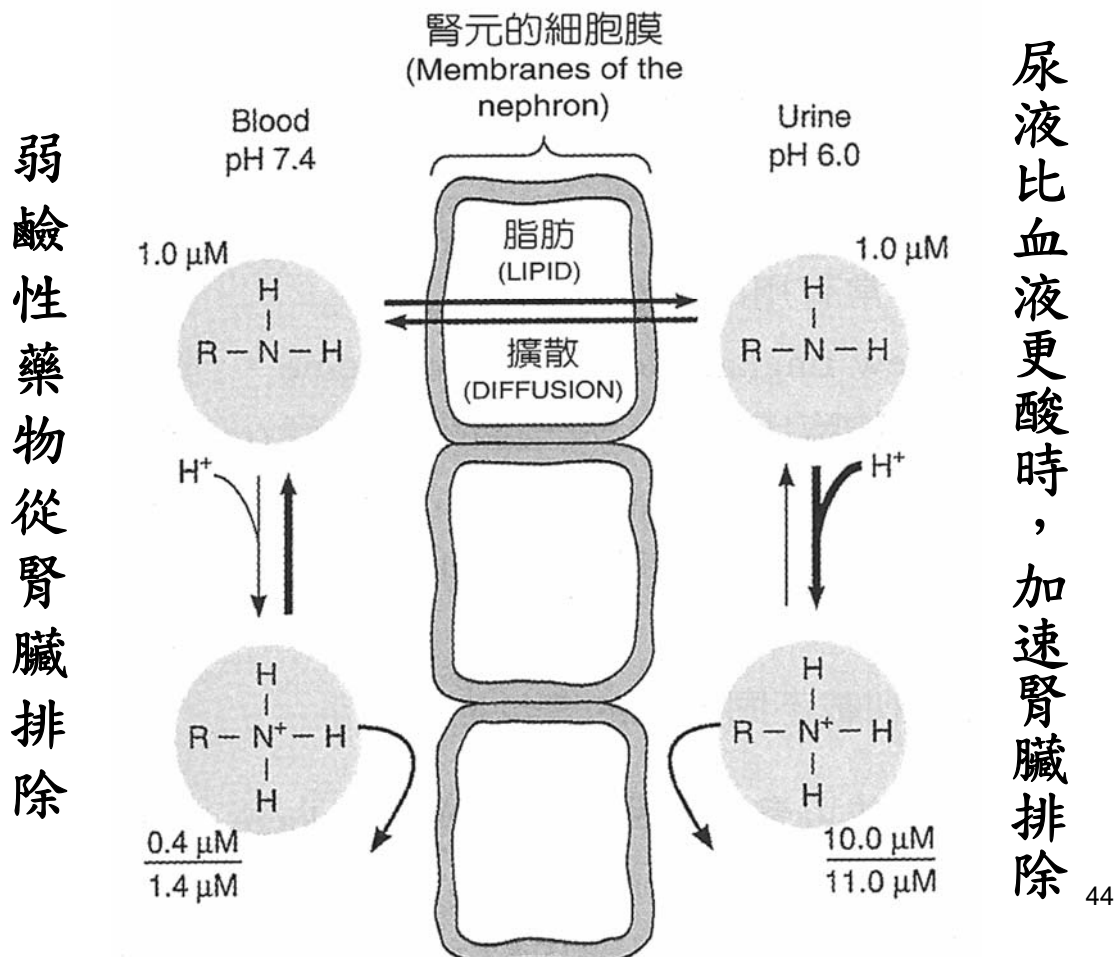
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Ion Trapping離子捕捉效應

□ Kidney腎臟

- Nearly all drugs filtered at the glomerulus
- Most drugs in a lipid-soluble form will be absorbed by passive diffusion
- To increase excretion:
 - Change the urinary pH to favor the charged (ionized) form of the drug
- 1. Weak acids: excreted faster in alkaline pH (anion form favored)
- 2. Weak bases: excreted faster in acidic pH (cation form favored)

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<u>乳汁</u>			<u>血液</u>		
pH 6.8			pH 7.4		
(偏酸性)			(偏鹼性)		
(非解離態可通過細胞膜)					
解離	非解離		非解離	解離	
[I]	[U]		[U]	[I]	
酸性藥物	較低		較低	較高	
	0.5		1	2	
Total	1.5		3		

酸性藥物的乳汁濃度較血液為低

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<u>乳汁</u>			<u>血液</u>		
pH 6.8			pH 7.4		
(偏酸性)			(偏鹼性)		
(非解離態可通過細胞膜)					
解離	非解離		非解離	解離	
[I]	[U]		[U]	[I]	
鹼性藥物	較高		較高	較低	
	2		1	0.5	
Total	3		1.5		

鹼性藥物的乳汁濃度較血液為高

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TABLE 3.1—Passage of antimicrobial agents from the systemic circulation into

• 乳汁：血漿之藥物濃度比值 • 高比值代表乳汁藥物殘留高				Concentration ratio (milk ultrafiltrate:plasma ultrafiltrate)
Drug	pK _a	Milk pH	Theoretical	Experimental
Organic acids				
Benzyl penicillin (G)	2.7	6.8	0.25	0.13-0.26
Cloxacillin	2.7	6.8	0.25	0.25-0.30
Ampicillin	2.7, 7.2	6.8	0.26	0.24-0.30
Cephaloridine	3.4	6.8	0.25	0.24-0.28
Sulfadimethoxine	6.1	6.6	0.20	0.23
Sulfamethazine	7.4	6.6	0.58	0.59
Organic bases				
Tylosin	7.1	6.8	2.0	3.5
Lincomycin	7.6	6.8	2.83	2.50-3.60
Trimethoprim	7.6	6.5-6.8	2.8-5.3	2.90-4.90
Erythromycin	8.8	6.8	3.9	8.7
Kanamycin	(7.8)	6.8	3.1	0.60-0.80

- 弱酸性抗生素不易進入乳汁。
- 除了kanamycin (高極性)較難進入乳汁，其他弱鹼性抗生素較容易由血液進入乳汁。

47

獸醫藥理學之特點

❖ 藥物動力學之特點

❖ 中樞神經系統藥理之特點

❖ 產食動物之內分泌藥理

中樞神經系統藥理之特點

- ❖ α_2 -agonist tranquilizers
 - ⌘ Human drug: anti-hypertensive
 - ⌘ Animal drug: pre-anesthetic medication, chemical restraint, anxiety
- ❖ Dissociative anesthetics
- ❖ Opioids for wild animals
- ❖ Antidepressants
 - ⌘ Human: major depression
 - ⌘ Animal: behavioral modification

49

Tranquilizer Nomenclature

- ❖ Major tranquilizers 寧神劑 =
Neuroleptics 精神安定劑 =
Antipsychotics 抗精神病藥 =
Antischizophrenics 抗精神分裂症藥物
 - ⌘ Phenothiazines
 - ⌘ Butyrophanones
 - ⌘ Thioxanthenes
- ❖ Minor tranquilizers
 - ⌘ Benzodiazepines

+

α_2 -Adrenergic
agonists
動物用寧神劑

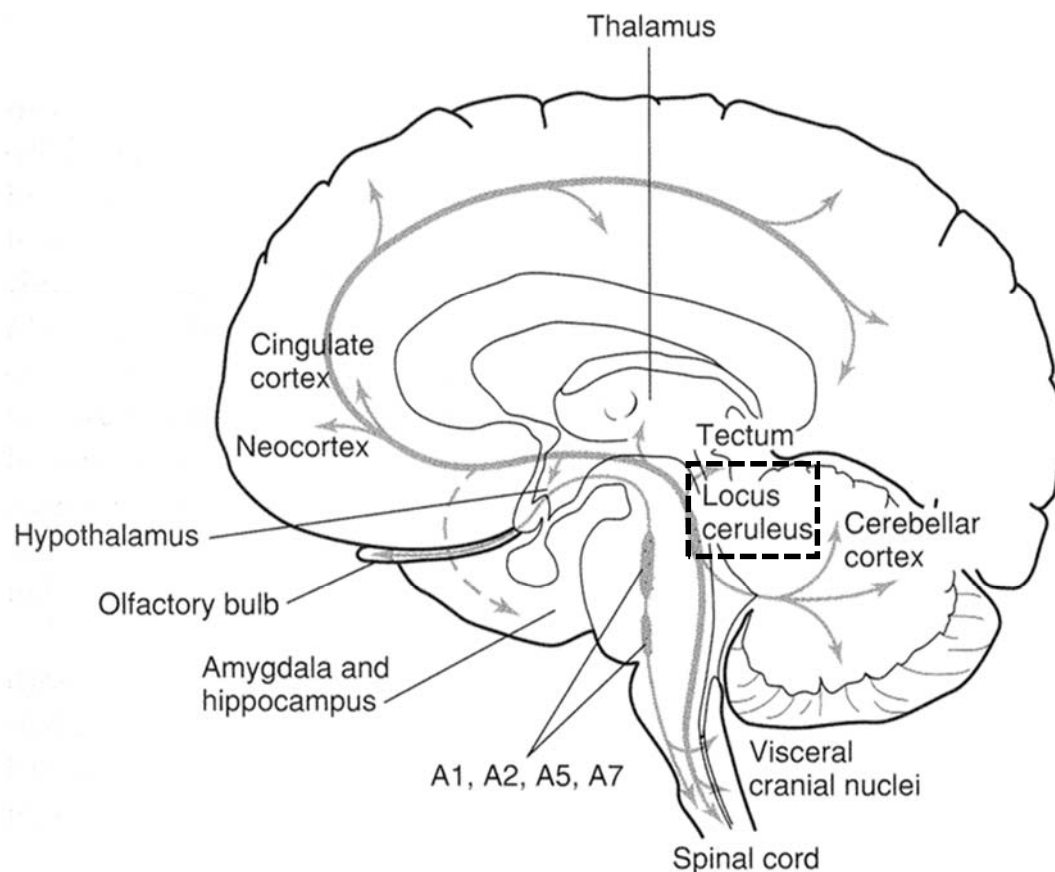
50

Drugs Used in General Anesthesia

Anesthetic process	Medication
Preanesthetic medication	Narcotic analgesics: morphine, fentanyl Sedatives: diazepam (minor tranquilizer) <i>Major tranquilizers: phenothiazines,</i> α_2 -adrenergic agonists Anticholinergic drugs: atropine
Induction	Injectable or inhalational anesthetics
Maintenance	Inhalational anesthetics: halothane Muscle relaxants: tubocurarine
Recovery	Narcotic analgesics: morphine Antibiotics

51

Only a few thousand neurons in the brain make NE



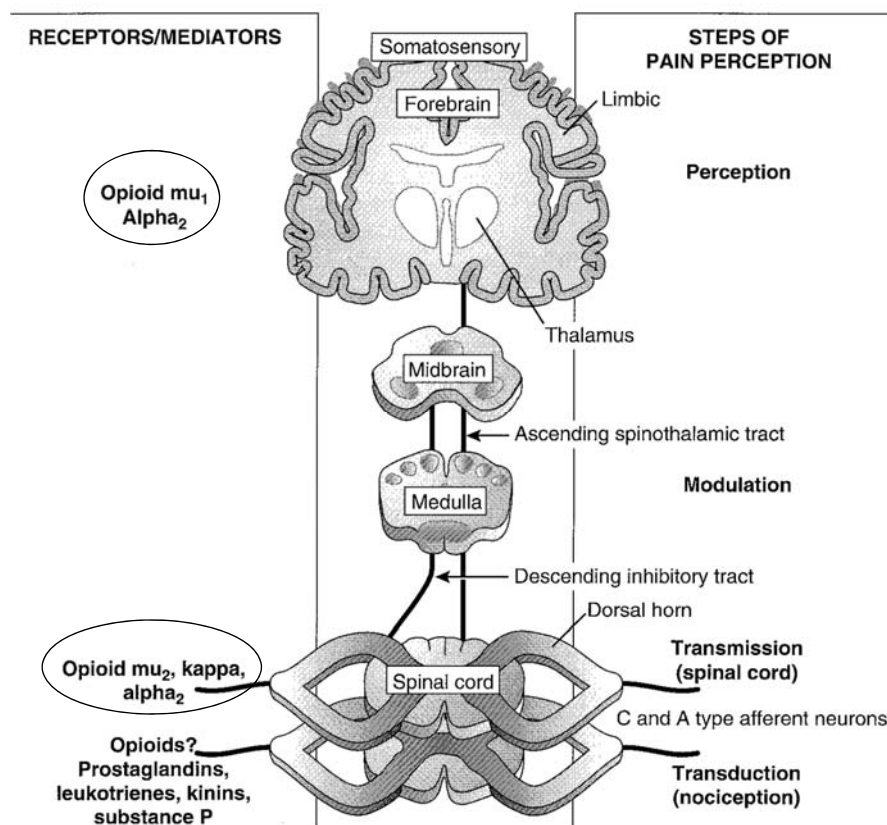
52

Norepinephrine (NE) in the Brain

- Cell bodies of NE neurons are located in brainstem (locus ceruleus & medulla)
- 1. Axons project widely throughout the brain
 - Release of NE produces an alerting, focusing, orienting response
 - Also involved in basic instinctual behaviors (hunger, thirst, emotion...)
 - Exposure to stressors increases NE release from the locus ceruleus
- 2. NE axons also project to the dorsal horn of the spinal cord, which produces analgesia

53

Pain Pathways & Receptors



54

α_2 -Agonist Human Drugs

- ❖ α_2 receptors are autoreceptors mediating **negative feedback in the brain**
- ❖ α_2 -adrenergic agonists decrease the central sympathetic outflow
- ❖ α_2 receptors are also expressed in blood vessels that promotes **vasoconstriction**
- ❖ **Clonidine** is a centrally acting antihypertensive drug in humans
- ❖ **Methyldopa** is metabolized to methyl-NE that activates α_2 receptors

55

α_2 -Adrenergic Agonists

- ❖ α_2 receptor: **CNS, cardiovascular, renal, GI...**
- ❖ **Agonists used as veterinary drugs**
 - ⌘ **Xylazine, detomidine, medetomidine, romifidine (horse), dexmedetomidine**
- ❖ **Antagonists: yohimbine, tolazoline...**
- ❖ **Central α_2 receptor stimulation results in**
 - ⌘ **Sedation/tranquilization**
 - ⌘ **Potent analgesia**
 - ⌘ **Decreased sympathetic outflow**
 - ⌘ **Muscle relaxation**

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α_2 -Agonist Vet Drugs

❖ Xylazine

- ❧ Tranquilization, analgesia & muscular relaxation
- ❧ Used as an emetic in cats

許可證字號：動物藥製字第08987號

動物用藥品名稱：舒痛安

英文名稱：SUTOIN

業者名稱：瑞立化學製藥股份有限公司

劑型：注射劑(注射劑)

包裝：50ML · 100ML · 10ML · 20ML

效能(適應症)：牛、馬、犬、貓之鎮靜，鎮痛，**麻醉**，肌肉鬆弛。

成分：EACH ML CONTAINS :
XYLAZINE (as HCL) 20MG

57

α_2 -Adrenergic Agonists

➤ Cardiopulmonary effects

- ❖ Bradycardia
- ❖ Negative inotropic effect: decrease cardiac output
- ❖ Xylazine *biphasic effect on blood pressure*: transient initial hypertension (peripheral α_1 & α_2 effect) followed by prolonged hypotension (central α_2 effect)
- ❖ Mild respiratory depression alone

58

α_2 -Agonists -- Other Effects

- ❖ **Decrease GI activity**
- ❖ **Cause vomiting in dogs (30%) & cats (90%) -- emetic center stimulation**
- ❖ **Abortion in cattle (not seen in horses)**
- ❖ **Hyperglycemia ($\downarrow$ insulin release)**
- ❖ **Depress thermoregulatory control**
 - ⌘ **Depend on ambient air temperature**
- ❖ ***Horses may kick unexpectedly (xylazine)***

59

Clinical Uses of α_2 -Agonists

- ❖ **Chemical restraint: *dependable sedation***
 - ⌘ **Preanesthetic medication**
 - ⌘ **In combination with ketamine or tiletamine**
- ❖ **Provide analgesia**
- ❖ **Provide muscle relaxation**
- **Pharmacological reversal by using α_2 -antagonists (yohimbine, tolazoline & atipamezole)**

60

Xylazine

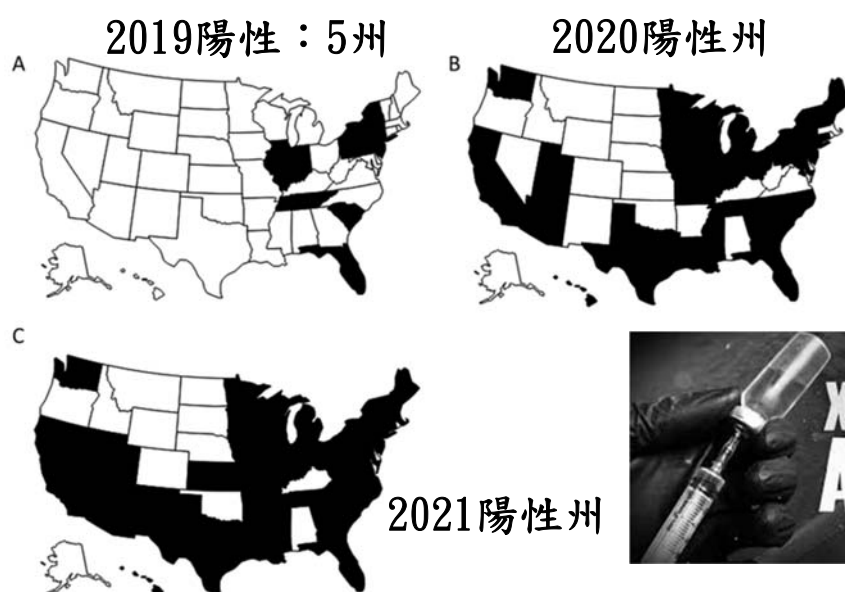
- ❖ Used in dogs, cats, horses, ruminants, avian & exotic species
- ❖ Potent analgesic activity
 - ⌘ Acting on α_2 -adrenergic receptors, not opioid receptors
 - ⌘ Not antagonized by naloxone
- ❖ Ruminants (cattle) are very sensitive; *dose is 1/10* of dogs, cats and horses
- ❖ Synergism with etorphine, fentanyl & ketamine
 - ⌘ Provide chemical restraint

61

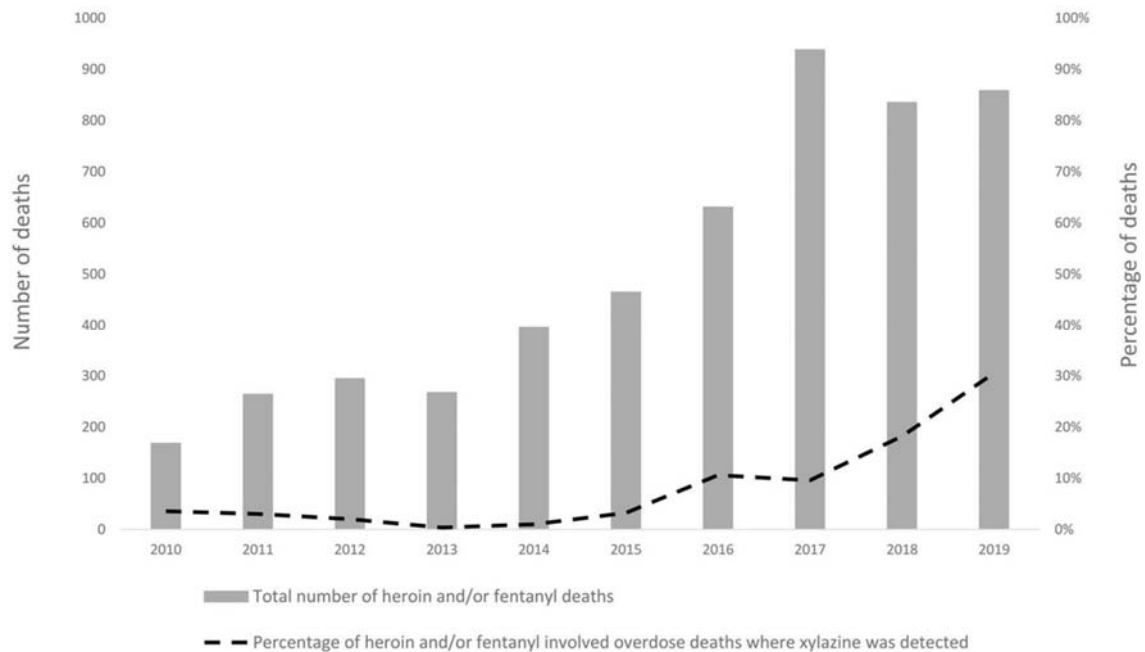
Xylazine – 全球新興濫用藥物

Journal of Analytical Toxicology, 2022, 46, 911–917

❖ 陽性案例持續上升



Overdose deaths involving xylazine in Philadelphia, Pennsylvania, 2010–2019



Jewell Johnson et al. Injury Prevention 2021;27:395-398

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Xylazine

(Horse Tranquilizer Drug)

Side Effects on Humans



- Skin lesions, sores, or infections
- Respiratory depression
- Decrease in blood pressure
- Hyperglycemia (high blood glucose)
- Blurred vision
- Disorientation and staggering
- Inability to respond
- Unconsciousness or sedation
- Coma
- Death from overdose



- ❖ Skin-rotting drug 'tranq' infiltrates big cities: 'Zombifying bodies'
 - ❖ Xylazine + heroin
 - ❖ Xylazine + fentanyl
 - ❖ Severe skin ulcers
- ☞ Skin perfusion ↓↓
- Synergism**

製造廠名稱: ORION CORPORATION

地址: ORIONINTIE 1, 02200 ESPOO, FINLAND

劑型: 注射劑(注射劑)

包裝: 10毫升

效能(適應症): 對於犬貓進行非侵入性、溫和至中度疼痛的手術和檢查時
犬隻誘導與維持全身麻醉前的預先用藥。

成分: DEXAMEDETOMIDINE HYDROCHLORIDE 0.5毫克
(相當於DEXAMEDETOMIDINE 0.42毫克)

核發日期: 中華民國98年11月25日

有效期間: 至107年12月01日止

對於犬貓進行非侵入性、溫和至中度疼痛的手術和
檢查時，提供其抑制、鎮靜與止痛的功效。另外，
可作為犬隻誘導與維持全身麻醉前的預先用藥

65

Epidural Analgesia in Animals

❖ **Commonly used in cattles, cats & dogs**

❖ **Opioids**

 ☞ Morphine, meperidine, fentanyl,
 buprenorphine

❖ **Local anesthetics**

 ☞ Lidocaine, ropivacaine, bupivacaine

❖ **α_2 -Adrenergic agonists**

 ☞ Dexmedetomidine

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Dexmedetomidine Human Use

西藥、醫療器材、化粧品許可證查詢
詳細處方成分 | 藥物外觀 | 仿單/外盒資料 | 授權使用 | 健保藥價查詢 | 離開
許可證詳細內容

*** 衛署藥輸字第024002號 ***

在加護病房治療期間初接受插管及人工呼吸器照護病人之鎮靜作用、非插管病人接受手術或其他程序前及/或手術或程序進行中之鎮靜作用，無論上述何種情況，靜脈輸注投與Precedex的時間，皆不得超過24小時

註銷狀態	
註銷理由	
有效日期	
許可證種類	
舊證字號	
通關簽審文件編號	
中文品名	
英文品名	
適應症	
劑型	
標籤、仿單及包裝加註	
藥品類別	05限由醫師使用
管制藥品分類級別	
藥品分類	
監視期限	
主成分略述	DEXMEDETOMIDINE HYDROCHLORIDE

67

中樞神經系統藥理之特點

- ❖ α_2 -agonist tranquilizers
 - ⌘ Human drug: anti-hypertensive
 - ⌘ Animal drug: pre-anesthetic medication, chemical restrain, anxiety
- ❖ Dissociative anesthetics
- ❖ Opioids for wild animals
- ❖ Antidepressants
 - ⌘ Human: major depression
 - ⌘ Animal: behavioral modification

K他命: 注射用麻醉劑

Synapse. 2011 February ; 65(2): 160–167. doi:10.1002/syn.20830.

A BEHAVIORAL AND MOLECULAR ANALYSIS OF KETAMINE IN ZEBRAFISH

Sherry M. Zakhary¹, Diana Ayubcha¹, Farah Ansari¹, Kiran Kamran¹, Mehwish Karim¹, Joerg R. Leheste¹, Judith M. Horowitz², and German Torres^{1,*}

¹Department of Neuroscience and Histology, New York College of Osteopathic Medicine of New York Institute of Technology, Old Westbury, New York, 11568, USA

²Clinical Neuroscience Laboratory, Medaille College, Buffalo, New York 14214, USA

❖ 廣泛使用於犬、貓、兔、羊、牛、豬、馬、禽類和魚類……

❖ 鱒魚肌肉注射

69

Ketamine之效能

許可證字號: 動物藥製字第08506號

動物用藥品名稱: 卡易眠100

英文名稱: KARSOON MINE 100

業者名稱: 公源藥品股份有限公司觀音廠

劑型: 注射劑(注射劑)

包裝: 20ML · 100ML · 50ML · 10ML

效能(適應症): 適於各種非經濟動物之:1.手術前、手術時之麻醉。2.運輸、保定及短時間之鎮靜。3.小手術、選擇性(局部)手術或急救情況下之麻醉。4.剖腹產手術之麻醉。5.高危險性病畜之麻醉。

各種非經濟動物之麻醉；運輸、保定及短時間之鎮靜

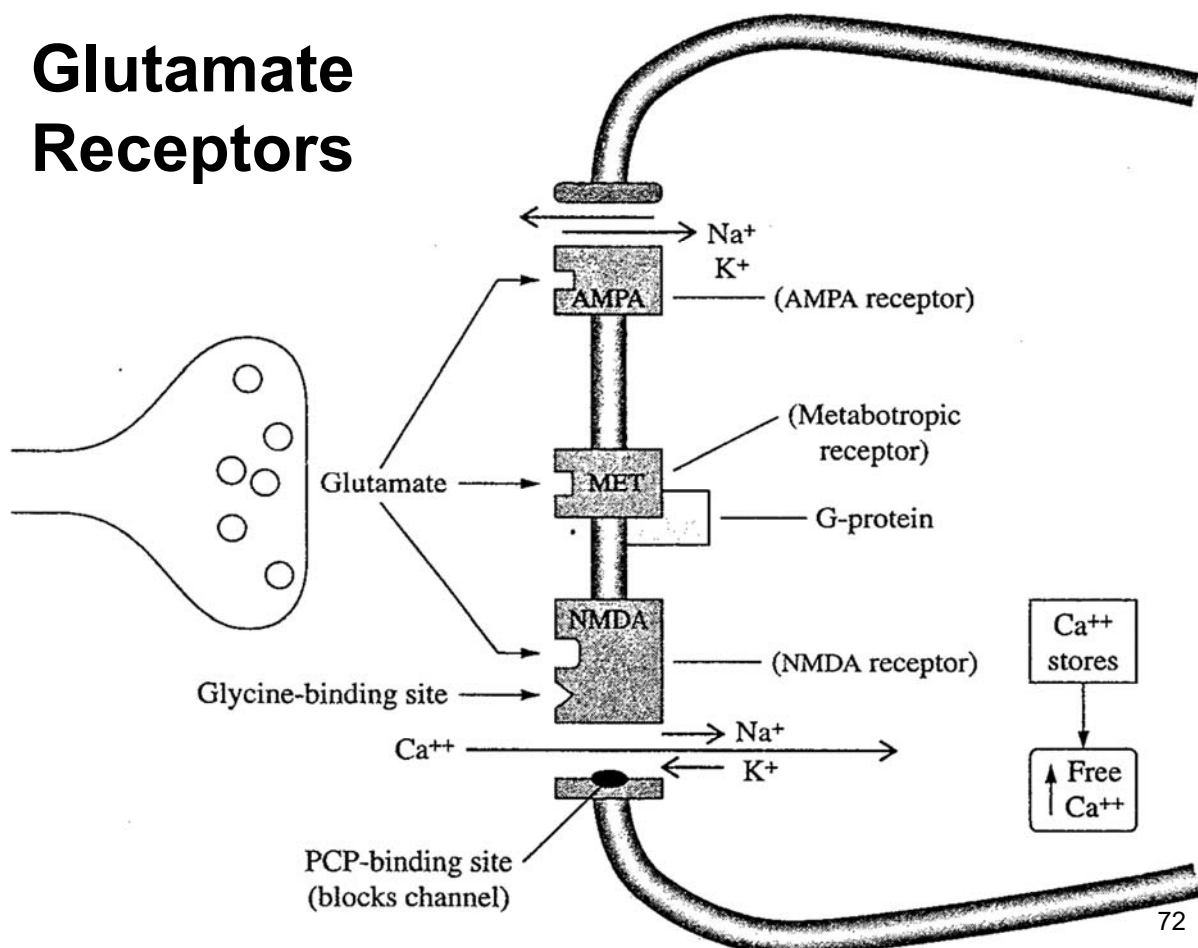
70

Glutamate and Aspartate

- ❖ **Glutamate & aspartate are found in high concentrations in the brain**
- ❖ **Both have powerful excitatory effects on neurons in the CNS**
- ❖ **Turnover cycle**
 - ⌘ **Synaptic glutamate is transported into astrocytes and convert to glutamine**
 - ⌘ **Glutamine is stored or diffuses out of astrocytes and then enter presynaptic terminals for glutamate production**

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Glutamate Receptors

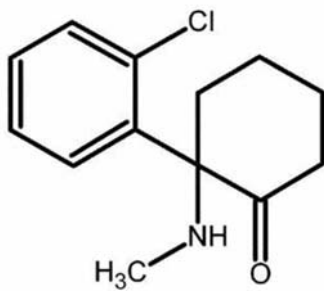


72

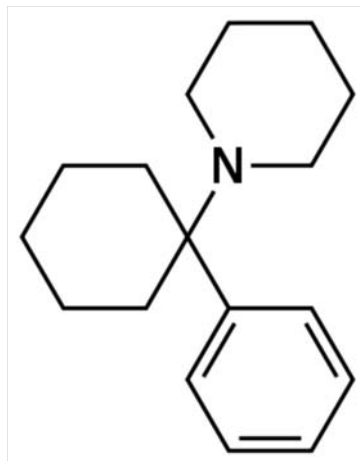
Glutamate Receptors

- ❖ **Metabotropic:** coupled to G-protein
- ❖ **Ionotropic:** ligand-gated ion channels
 - ∞ **AMPA receptors**
 - ❖ Na^+ & K^+ permeable
 - ❖ Limited Ca^{++} permeability
 - ∞ **NMDA receptors**
 - ❖ Highly Ca^{++} permeable
 - ❖ $\text{Ca}^{++} : \text{Na}^+ : \text{K}^+ = 20 : 1 : 1$
- ⊕ **AMPA:** α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
- ⊕ **NMDA:** *N*-methyl-*D*-aspartate

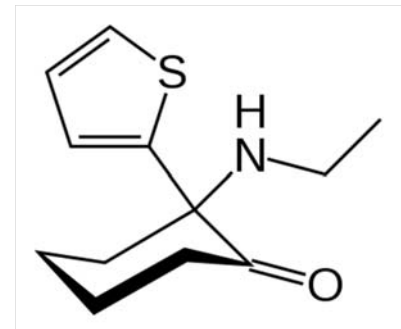
73



Ketamine



Phencyclidine



Tiletamine

- **1-(1-phenylcyclohexyl)piperidine: PCP**
- **An hallucinogen: angel dust**
- **Many adverse effects: mania, delirium...**
- **Slow elimination rate: several days**

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Dissociates: Ketamine & Tiletamine

- **Mechanism of action** 拮抗NMDA受體
 - Noncompetitive antagonists to NMDA (N-methyl-D-aspartate) receptors
- **Pharmacological effects**
 - Produce dissociate anesthesia
 - Clinical doses stimulate sympathetic system ⇒ Cardiovascular stimulation
 - Large doses depress myocardium directly ⇒ Hypotension

75

Dissociative Anesthesia (Cataleptic State)

- In a hypnotic state
- Profound analgesia
- Seem to be awake but unaware of the environment (dissociated from environment)
- Eyes open
- Spontaneous respiration
- The animal maintains pharyngeal, laryngeal, corneal and swallowing reflexes
- Increase muscle tone (limb movement)
- Increase salivation & lacrimation

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Dissociatives: Ketamine & Tiletamine

- **Route of administration: IM & IV**
 - **Used in cats & many wild animals for chemical restraint or anesthesia**
 - **Other anesthetics are ineffective via IM**
- **Require suitable preanesthetic medications**
 - **A tranquilizer to prevent involuntary movement**
- **Ketamine: used as human & animal drugs**
- **Tiletamine: only veterinary use**

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Ketamine Preanesthetic Medication

- **Cats:** promazine + aminopentamide + ketamine (Ketaset® Plus)
 - Major tranquilizer
- **Dogs:** diazepam, midazolam or medetomidine
 - Minor tranquilizer
 - α_2 -agonist (tranquilizer)
- **Horses:** xylazine or detomidine
 - α_2 -agonist (tranquilizer)
- **Large animals (horses & cattle):** guaifenesin
 - CNS sedative & muscle relaxant
- **Exotic large animals**
 - Telazol®: tiletamine + zolazepam
 - CNS sedative (minor tranquilizer)
 - Zoletil®

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Opioids for Wild animals

- ❖ **α_2 -agonist tranquilizers**
 - ❧ Human drug: anti-hypertensive
 - ❧ Animal drug: pre-anesthetic medication
- ❖ **Dissociative anesthetics**
- ❖ **Opioids for wild animals**
 - ❧ Fentanyl
 - ❧ Carfentanil
 - ❧ Etorphine

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Fentanyl and Derivatives

- ❖ **Fentanyl: human & animal drug**
 - ❧ Potency 100x of morphine
 - ❧ Analgesia: 2-50 $\mu\text{g/kg}$ in human
 - ❧ Transdermal patch: 25 $\mu\text{g/h}$
- ❖ **Sufentanil: human & animal drug**
 - ❧ Potency 5-10x of fentanyl
 - ❧ Analgesia: 0.5-5 $\mu\text{g/kg}$ in human
 - ❧ Parenteral: IV, IM, SC, epidural
- ❖ **Carfentanil: animal drug only**
 - ❧ Potency: 100x of fentanyl = 10000x morphine
 - ❧ Used in large wild animals

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Carfentanil

- ❖ **Potency: 10000x of morphine**
- ❖ **Used for immobilization of large zoo & wildlife species, except for horses (due to unacceptable adverse effects)**
- ❖ **US FDA approval for use in Cervidae 鹿科動物 (deer, elk & moose)**
- ❖ **Dose: IM 0.005-0.02 mg/kg via projectile dart 飛鏢、注射槍**
- ❖ **Variable $t_{1/2}$ (2-24 h): Use naltrexone (longer $t_{1/2}$), not naloxone as the antidote**

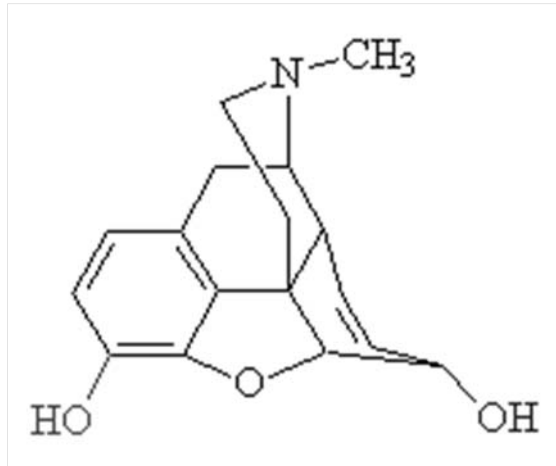
81

Etorphine (M99[®])

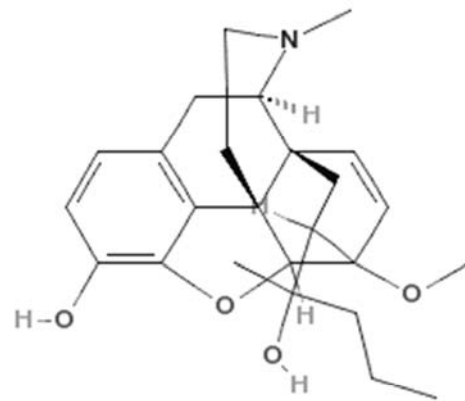
- ❖ **10000x analgesic potency of morphine**
- ❖ **IM administration results in rapid immobilization, sedation, and analgesia**
- ❖ **Used only when diprenorphine (M50[®]) or other suitable antagonists are available**
- ❖ **For use in wild or exotic animals only**
- ❖ **Dose for most exotic animals is 1- 2 mg**
 - ↻ **Zebra: 1.5 mg**
 - ↻ **African elephant: 6 mg**

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Morphine



Etorphine



www.ChemDrug.com

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Drugs for Use in Tranquilizer Dart 麻醉槍、吹箭

❖ Injectable anesthetics

↻ Ketamine

❖ α_2 -adrenergic agonists

↻ Detomidine, xylazine

❖ Opioids

↻ Carfentanil, etorphine

❖ Major tranquilizers

↻ Acepromazine, azaperone, haloperidol

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中樞神經系統藥理之特點

- ❖ **α_2 -agonist tranquilizers**
 - ⌘ Human drug: anti-hypertensive
 - ⌘ Animal drug: pre-anesthetic medication, chemical restraint, anxiety
- ❖ **Dissociative anesthetics**
- ❖ **Opioids for wild animals**
- ❖ **Antidepressants**
 - ⌘ Human: major depression
 - ⌘ Animal: behavioral modification

85

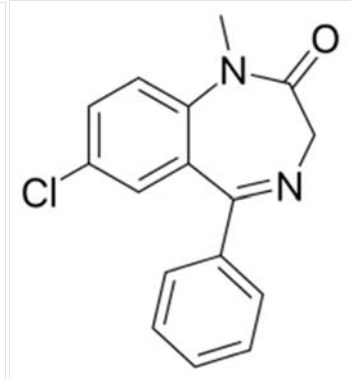
Drugs Used to Modify Behavior

- ❖ **Major tranquilizers & α_2 -adrenergic agonists**
- ❖ **Minor tranquilizers (benzodiazepines)**
- ❖ **Antidepressants**
 - ⌘ Tricyclic antidepressants (TCA)
 - ⌘ Selective serotonin reuptake inhibitors (SSRI)
- ❖ **CNS stimulants**
- ❖ **Miscellaneous drugs: nonspecific effects**
 - ⌘ Hormones
 - ⌘ Opioids: depression or excitation
 - ⌘ Antihistamines: sedation

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Minor tranquilizer: Benzodiazepines

- ❖ **Mechanism: GABA_A receptors**
- ❖ **CNS effects**
 - ⌘ **Anxiolytic activity**
 - ⌘ **Sedative**
 - ⌘ **Hypnotic**
 - ⌘ **Anterograde amnesia (FM2)**
 - ⌘ **Muscle relaxation**
 - ⌘ **Anticonvulsant activity**
 - ⌘ **No general anesthesia**



Diazepam

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Veterinary Uses of BZD

1. **Preanesthetic medication**
 - ⌘ **Smooth induction & recovery of anesthesia**
 - ⌘ **Combined with other agents (i.e. ketamine)**
2. **Seizure disorders (anticonvulsants)**
 - ⌘ **Diazepam IV bolus: rapid entering into the brain for status epilepticus**
3. **Anti-anxiety**
 - ⌘ **Behavioral modification in cats & dogs**
 - ⌘ **Appetite enhancement in cats**

88

Pet Behavioral Disorders

- ❖ **A common reason for pets to visit DVM**
- ❖ **A common cause of frustration for pet owners**
- ❖ **Also a common cause of euthanasia**
 - ⌘ **Unacceptable or dangerous behavior**
- ❖ **Many antidepressants are not approved for use in animals, but used by veterinarians as extra (off)-label drugs 標籤外使用**
 - ⌘ **Use drugs not in accordance with the approved label directions**

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Veterinary Uses of BZD

- 3. Behavioral modification (anti-anxiety)**
 - ⌘ **Dog & cat: management of fears, phobia, inappropriate urination & separation anxiety; particularly suitable for those can be predicted**
 - ⌘ **Dog: noise aversion**
 - ⌘ **Cat: ↑appetite (diazepam)**
 - ⌘ **Mink: anxiety & aggressiveness (↑mating & breeding)**

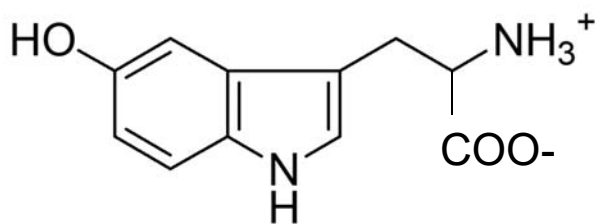
90

Antidepressants

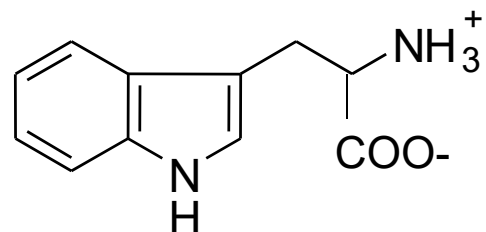
- ◆ **Tricyclic antidepressants (TCA)**
- ◆ **Selective serotonin reuptake inhibitors (SSRI)**

91

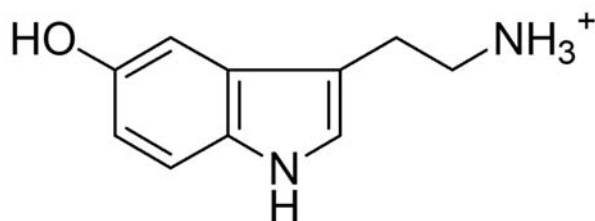
5-HT



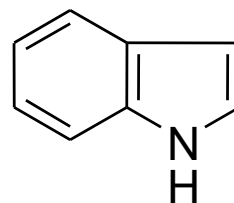
5-hydroxytryptophan



Tryptophan



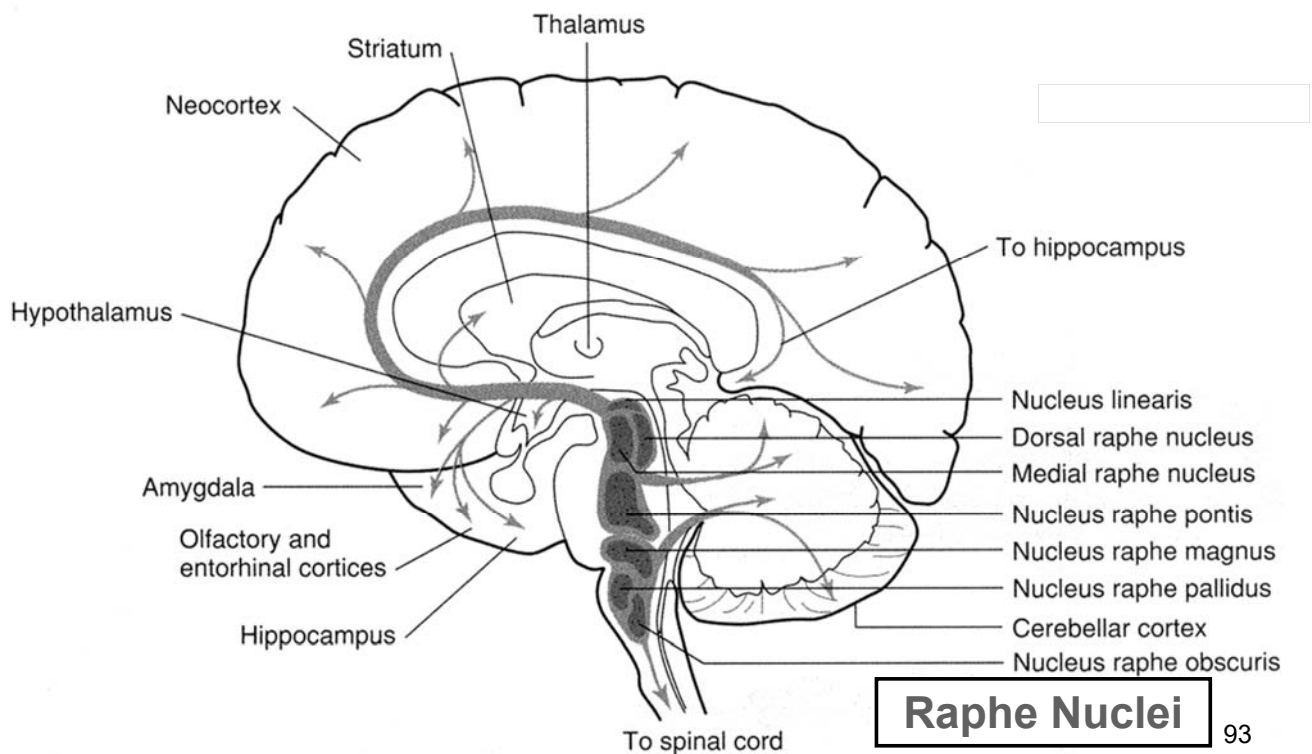
**5-hydroxytryptamin
(5-HT)**



Indole

92

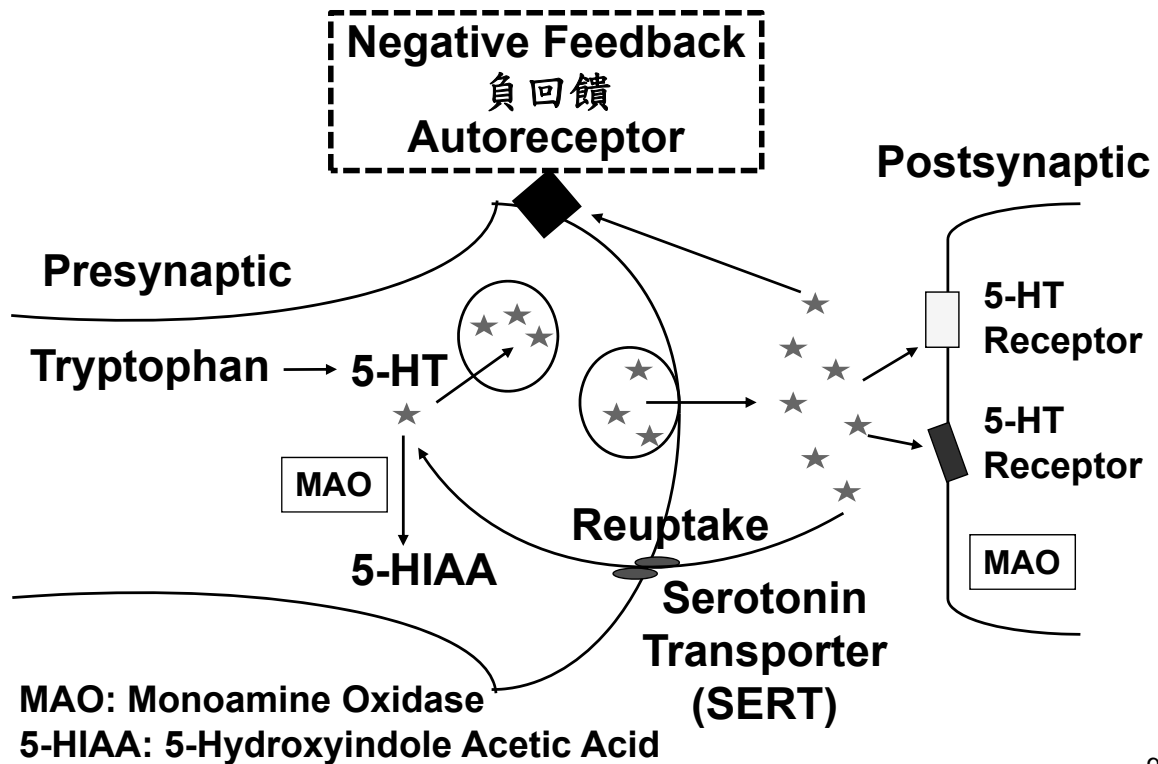
Serotonin Projection to Many Higher Brain Regions



Overview of 5-HT Neurotransmission

- **Cell bodies of serotonergic neurons locate in the raphe nuclei (RN) of the midline brainstem**
- **Dorsal and median RN**
 - Projection to thalamus, hypothalamus, basal ganglia & forebrain
 - Involved in the regulation of **behavioral state**
- **Pontine and medullary RN**
 - Projection to brainstem, cerebellum & spinal cord
 - Modulation of sensory input and motor control
- **Physiological processes regulated by 5-HT**
 - **Mood, sleep, sexual drive, gastrointestinal motility, platelet aggregation and vasoconstriction**

5-HT Synapse Turnover



95

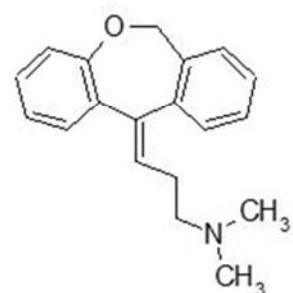
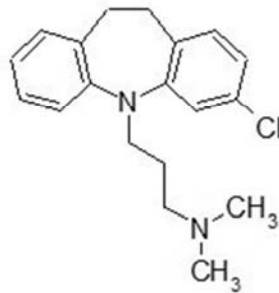
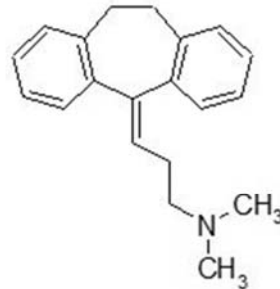
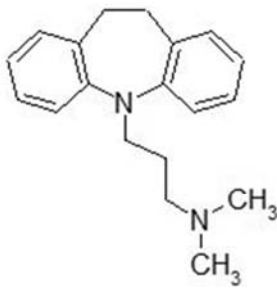
5-HT Hypothesis of Major Depression

▪ Major depression is associated with abnormal 5-HT neurotransmission

1. Tryptophan level is diminished in depressed patients
2. Tryptophan-free diets produce mood-lowering effects
3. Intake of tryptophan elicits antidepressant effect
4. Lower brainstem levels of 5-HT, 5-HIAA and SERT binding sites were observed in depressed suicide victims
5. Therapeutic antidepressants interfere with 5-HT neurotransmission

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Tricyclic Antidepressants



Imipramine clomipramine amitriptyline doxepin

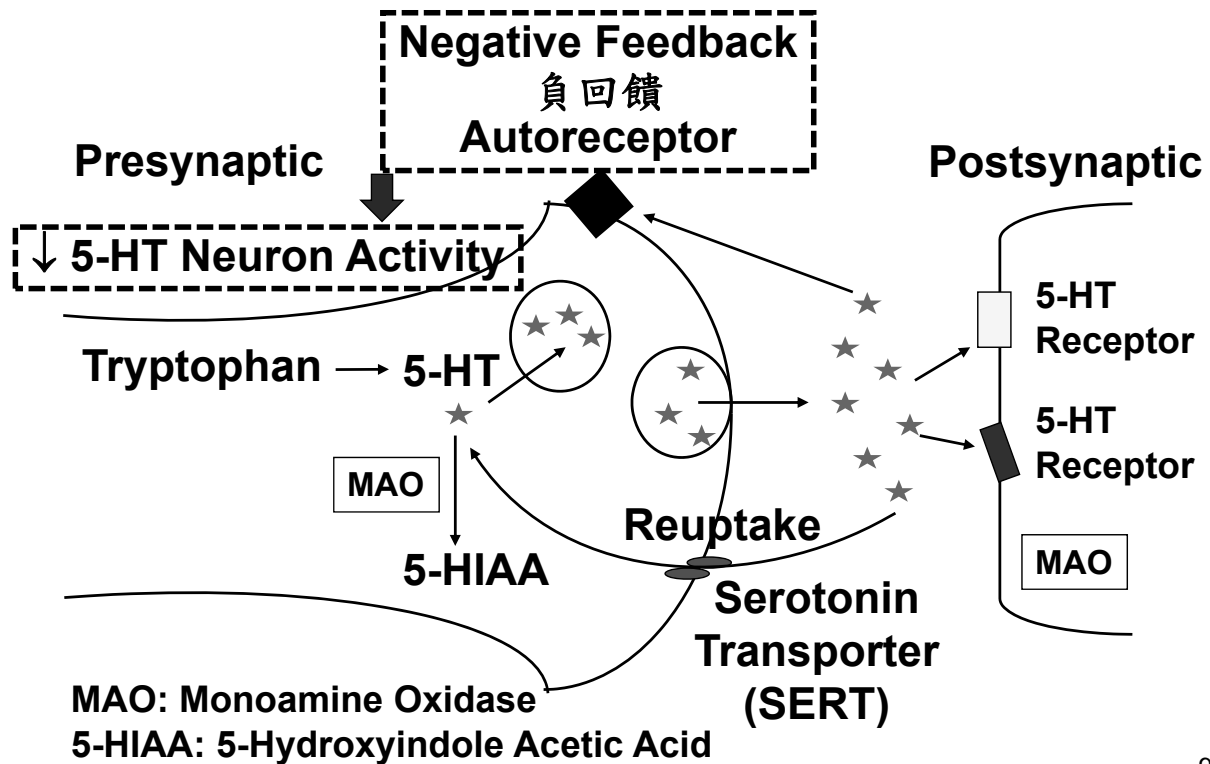
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Tricyclic Antidepressants & SSRI

- **Tricyclic antidepressants (TCA) block neuronal reuptake of 5-HT & NE (but not DA)**
- **Imipramine, clomipramine, amitriptyline, doxepin**
- **Frequently prescribed in human medicine**
- **Extra-label use drugs in vet medicine**
- **The clinical effectiveness (~70%) of TCA and SSRI indicates that SERT plays a pivotal role in the pathophysiology of depression**
- **Delayed onset of therapeutic effects: > 3 weeks**

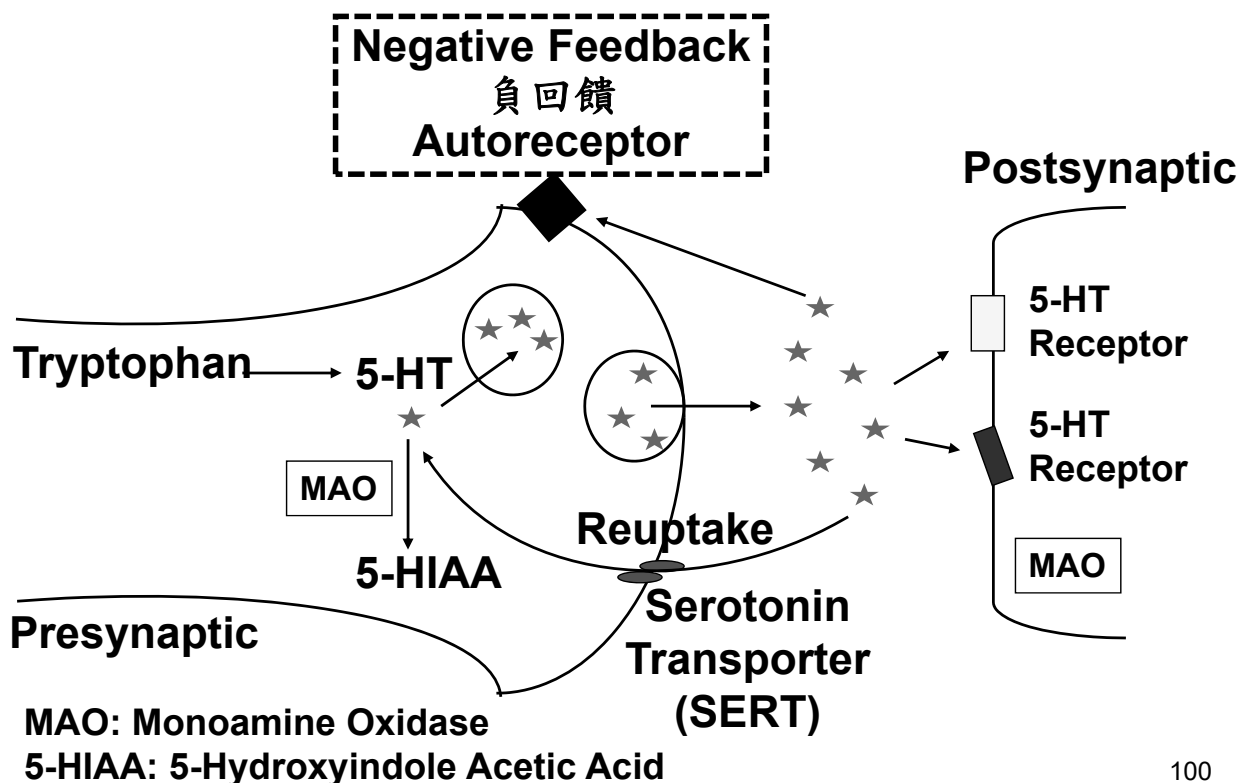
98

5-HT Synapse Turnover



99

5-HT Synapse Turnover



100

TCA - Clomipramine

- ❖ **Most selective 5-HT reuptake inhibitor in TCA**
- ❖ **FDA approval: separation anxiety in dogs in combination with other drugs**
- ❖ **Other indications: abnormal behaviors (aggression, fear, excessive barking), compulsive behavior, various anxious states, inappropriate urination and spraying behavior in dogs & cats**

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SSRI

- ❖ **SSRI are selective inhibitors for SERT**
- ❖ **Fluoxetine, paroxetine, sertraline, fluvoxamine**
- ❖ **Fluoxetine (Prozac®) is widely prescribed for major depression treatment in human**
- ❖ **Vet use: anxiety, aggression, compulsive disorders, urine marking...**
- ❖ **Onset: > 3 weeks due to down-regulation of 5-HT_{1A} autoreceptors**
- ❖ **Excellent safety: fewer side effects than TCA**

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Noise Aversion (Phobia) in Dogs



<https://www.zoetis.co.uk/sileo/noise-anxiety.aspx>

103

Noise Aversion (Phobia) in Dogs

- ❖ 恐音症：Affects one-third of dogs in the U.S.
- ❖ Patients experience fear and anxiety
 - ⌘ 對噪音的恐懼和焦慮反應
 - ⌘ Similar to a panic attack in humans
- ❖ Therapeutic drugs
 - ⌘ Benzodiazepines (alprazolam, diazepam),
 - ⌘ SSRI (fluoxetine 百憂解)
 - ⌘ Clomipramine 三環抗憂鬱劑
 - ⌘ Dexmedetomidine (oromucosal gel 口腔黏膜凝膠)
 - ❖ An $\alpha 2$ -agonist

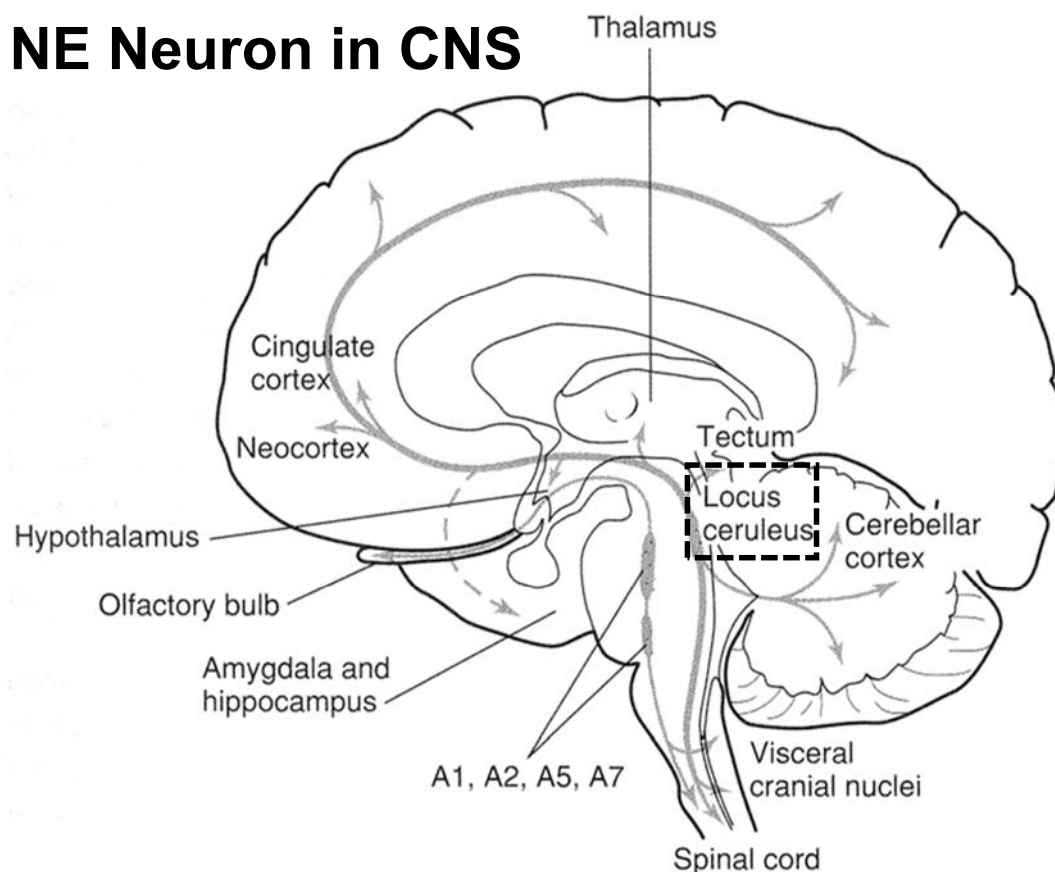
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Dexmedetomidine for Canine Noise Aversion

- ❖ **Oromucosal gel approved by US FDA for the treatment of canine noise aversion in 2016**
- ❖ **Dexmedetomidine is a potent α_2 -agonist**
 - ⌘ **The locus ceruleus mediates stress and anxiety, fear learning and memory**
 - ⌘ **Exposure to stressors (i.e. noise) increases NE release from the locus ceruleus**
 - ⌘ **Dexmedetomidine activates α_2 receptors that reduces NE release in the locus ceruleus resulting in calming effect**

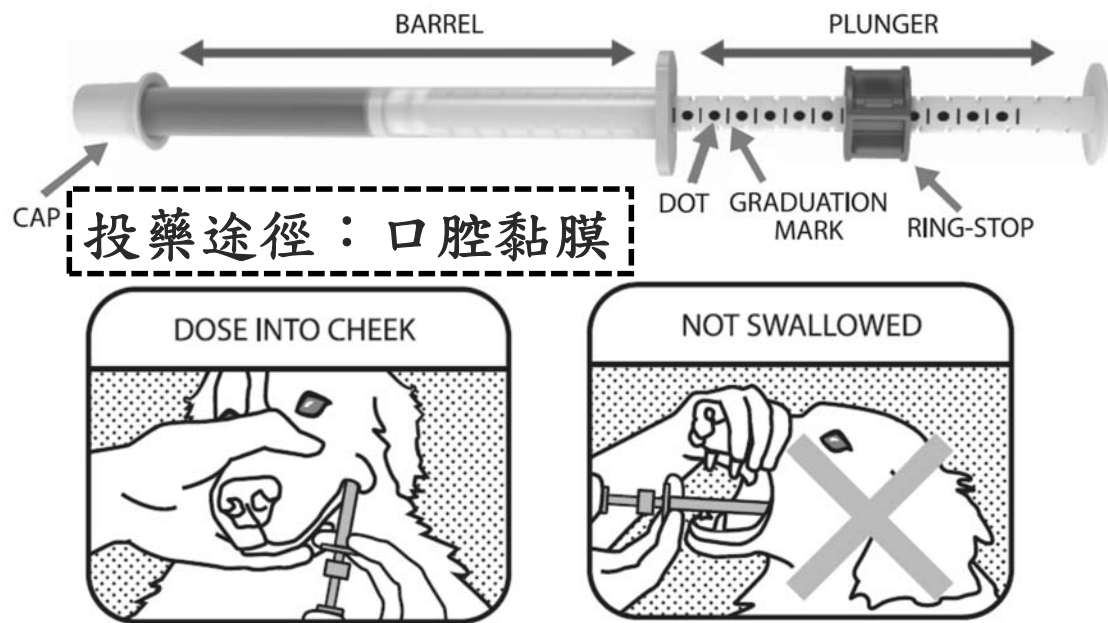
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NE Neuron in CNS



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Dexmedetomidine Oromucosal Gel 口腔黏膜凝膠 Syringe



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產食動物之內分泌藥理

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Endocrine Pancreas

A (or α)	~25%	Glucagon
B (or β)	~70%	Insulin
D (or δ)	<5%	Somatostatin
F	Trace	Pancreatic polypeptide

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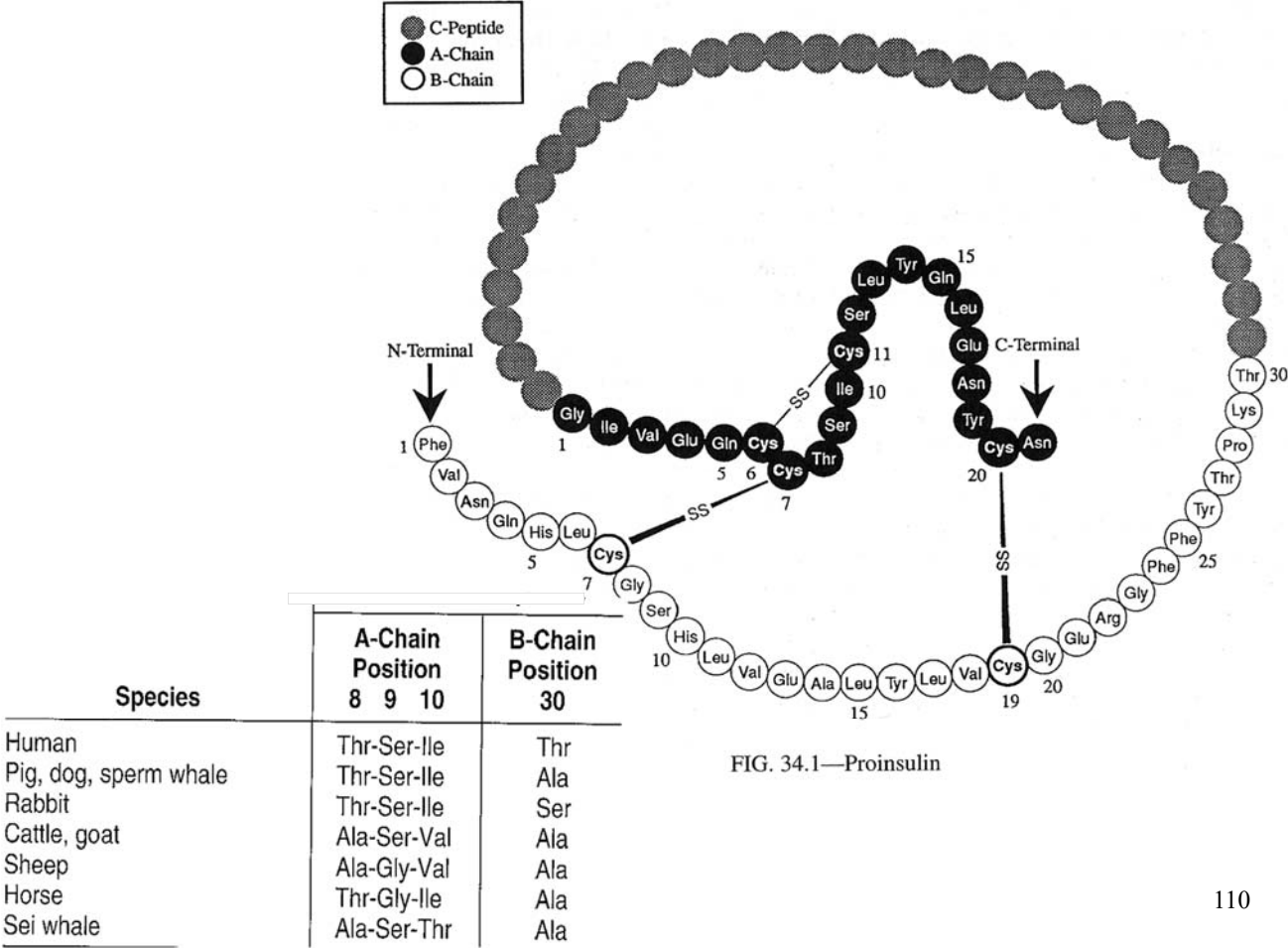


FIG. 34.1—Proinsulin

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Insulin Preparations for Animals

❖ Vetsulin® (Caninsulin®)

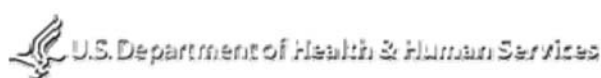
❧ **Porcine insulin zinc** for approved for use in dogs & cats

❖ PZI Vet®

❧ **Bovine (90%) & porcine (10%) insulin** approved for use in cats

❧ **Microcrystalline suspension: Complexed with protamine zinc**

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FDA Center for Veterinary Medicine

[Return To Search](#)

[Return To Results](#)

NADA Number: 141-236

Proprietary Name	Vetsulin® Vetsulin™
Sponsor	Intervet, Inc.
Sponsor Address	29160 Intervet Lane P.O. Box 318 Millsboro, DE 19966 USA
Ingredients	Porcine insulin zinc
Species	Cat, no use class stated Dog, no use class stated

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許可證字號：動物藥入字第06847號

動物用藥品名稱：健宜寧針劑

英文名稱：CANINSULIN

業者名稱：台灣英特威動物藥品股份有限公司

劑型：注射劑(滅菌懸劑)

包裝：2.5ML，2.7ML，10ML

效能(適應症)：犬、貓：治療犬、貓之糖尿病。

成分：EACH ML CONTAINS :
PORCINE INSULIN 40IU

核發日期：中華民國101年04月02日

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Use of Insulin in Dairy Cows

❖ Ketosis in cattle

❧ Occurs within the 1st week of lactation due to a negative energy balance

❖ Excessive metabolism of lipid

❧ Some are nonresponsive to glucose or glucocorticoid therapy

❧ Insulin is an effective antiketogenic drug

❧ An adjunct treatment in ketosis therapy

❧ 200-300 IU protamine zinc insulin per cow

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Anti-insulin Hormones

❖ Increase the level of blood glucose

❧ Glucagon

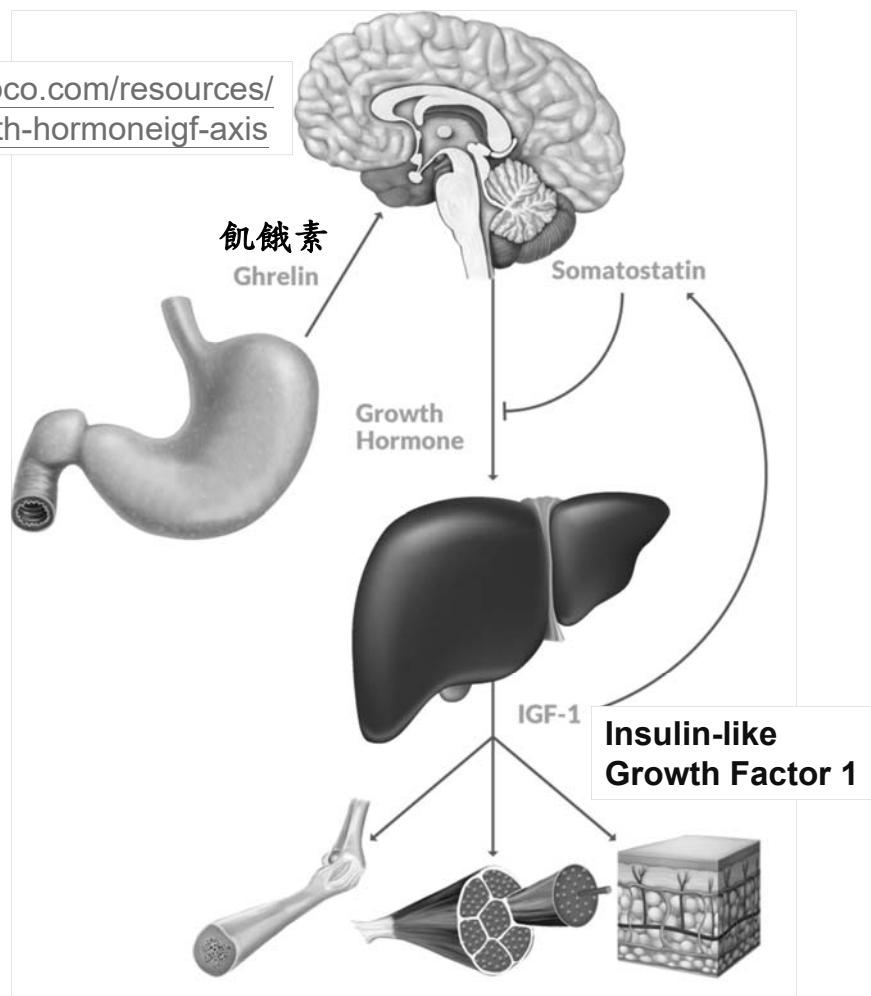
❧ Epinephrine

❧ **Growth hormone**

❧ Glucocorticoids

115

<https://www.alpco.com/resources/role-igf-1-growth-hormoneigf-axis>



116

Uses of GH in Animals

- **Increases milk production in dairy cows**
 - ⌘ **Sometribove**, prolonged-release injectable formulation of a recombinant DNA-derived bovine somatotropin analog
 - ⌘ **SC 500 mg/2 weeks**; from 9 weeks after giving birth
 - ⌘ **Used in USA**; banned in EU (milk [IGF-1])
- **Pituitary dwarfism in young dogs**
 - ⌘ **Porcine = canine GH**
 - ⌘ **0.1 IU/ kg, SC 3 times/week** for 4-6 weeks

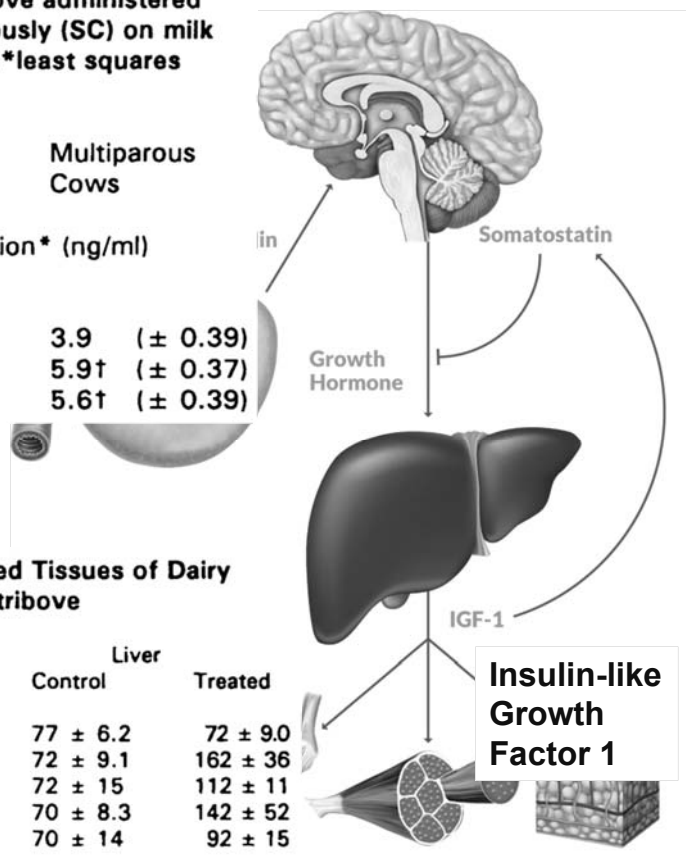
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Table 6. The effect of 500 mg of sometribove administered intramuscularly (IM) or subcutaneously (SC) on milk concentrations of IGF-I and IGF-II (*least squares means $\pm$ SEM).

Sampling Period	Primiparous Cows	Multiparous Cows
	Milk IGF-I Concentration* (ng/ml)	
Overall Cycle 1-10		
Control	3.5 ($\pm$ 0.67)	3.9 ($\pm$ 0.39)
IM	5.9† ($\pm$ 0.59)	5.9† ($\pm$ 0.37)
SC	6.1† ($\pm$ 0.60)	5.6† ($\pm$ 0.39)

Table 7. Concentration of IGF-I (ppb) in Biopsied Tissues of Dairy Cattle Injected with 500 mg of Sometribove

Withdrawal Time (days)	Muscle		Liver	
	Control	Treated	Control	Treated
0	80 $\pm$ 16*	91 $\pm$ 26	77 $\pm$ 6.2	72 $\pm$ 9.0
7	272 $\pm$ 160*	312 $\pm$ 130	72 $\pm$ 9.1	162 $\pm$ 36
14	252 $\pm$ 141	152 $\pm$ 62	72 $\pm$ 15	112 $\pm$ 11
21	68 $\pm$ 20	126 $\pm$ 58	70 $\pm$ 8.3	142 $\pm$ 52
28	215 $\pm$ 173	135 $\pm$ 19	70 $\pm$ 14	92 $\pm$ 15



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Estrogens

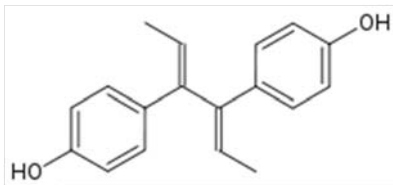
- ❖ **Many substances have estrogenic activity**
 - ❧ **Steroidal estrogens: animal sources**
 - ❖ **Estradiol (estradiol-17 β , E₂)**
 - ❖ **Estrone (E₁) & Estriol (E₃)**
 - ❧ **Nonsteroidal estrogens: synthetic**
- ❖ **Stimulate & maintain the reproductive system & the mammary gland**
- ❖ **Induce estrus**
- ❖ **Antagonize androgen effects**
- ❖ **Anabolic effect**
 - ❧ **Stimulate protein synthesis**
 - ❧ **Growth promotion in ruminants**

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Synthetic Estrogens

- ❖ **Chemical modifications of natural estrogens**
 - ❧ **Affect PK, increase duration of action**
- ❖ **Esters of estradiol (E₂)**
 - ❧ **Benzoate: ear implants for beef cattle**
 - ❧ **Cypionate: oil preparation for IM injection**
- ❖ **Side effects**
 - ❧ **Abortion, follicular cysts, bone fractures (due to excessive ossification)...**
 - ❧ **Bone marrow suppression (anemia, ↓WBC)**
 - ❖ **A unique toxic effect in dogs**

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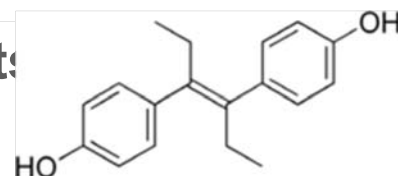
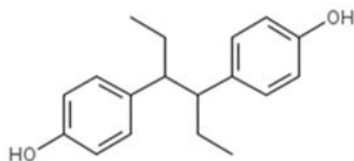


Synthetic Estrogens

❖ Nonsteroidal estrogenic agents

❧ **Dienestrol**

❧ **Hexestrol**



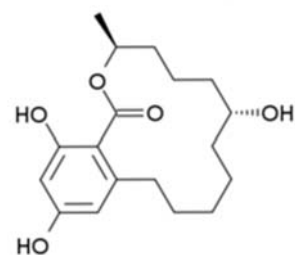
DES

❧ **Increased risk of endometrial cancer in postmenopausal women**

❧ **Zeranol**

❖ **A mycotoxin (mycoestrogen)**

❖ **Anabolic agent: used as a growth promoter in livestock**



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Progestins

❖ **Progestins = progesterone + synthetic analogs**

❖ **Inhibit estrus & extend the luteal phase**

❖ **Estrus appears several days a/f the last dose**

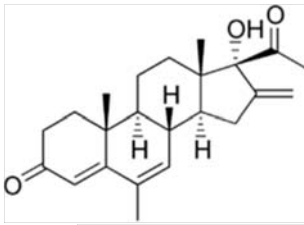
❧ **Synchrony in large animals (estrus cycle control)**

❧ **Mediated by ↑ gonadotropin secretion**

❖ **Prevent uterine contraction during pregnancy**

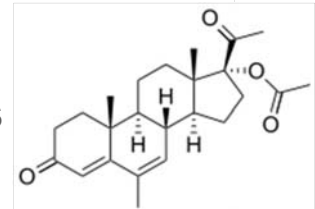
❖ **Exhibit anabolic effect due to increased appetite & decreased physical activity**

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Progestins

- ❖ **Melengestrol acetate: a growth promoter used as a cattle feed additive**
 - ⌘ Progesterone plus estradiol benzoate are also used as an ear implant for growth promotion
- ❖ **Megestrol acetate (MA)**
 - ⌘ A contraceptive in humans & bitches
 - ⌘ An appetite stimulant in humans
- ❖ **Hormonal therapy for behavior problems**
 - ⌘ Medroxyprogesterone acetate (MPA) & MA
 - ⌘ Control aggressiveness in dogs & cats



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Anabolic Agents

- ❖ **Estrogens**
 - ⌘ Estradiol esters, zeranol implants
- ❖ **Progestins**
 - ⌘ Progesterone implants
 - ⌘ Melengestrol as a feed additive
- ❖ **Androgens**
 - ⌘ Testosterone propionate implants
 - ⌘ Synthetic anabolic steroids
 - ❖ Stanozolol, boldenone, trenbolone

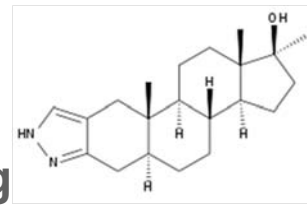
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Anabolic Androgenic Steroids

同化性雄性類固醇

❖ Stanozolol

- ❧ Weak androgenic activity
- ❧ A performance-enhancing drug
- ❧ Approved for used in humans & animals

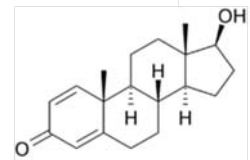


❖ Veterinary usage of stanozolol, boldenone

- ❧ ↑ Growth, anemia, tissue depletion

❖ Boldenone undecylenate injection

- ❧ FDA approval for debilitated horses



❖ Trenbolone (+E₂) ear implants

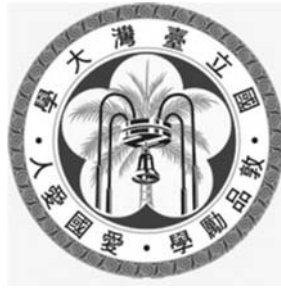
- ❧ Growth promoters for cattle 耳後皮下植入

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重點複習

- ❖ 威而鋼：cGMP; 肺高壓
- ❖ Ion trapping: urine pH & 藥物的排除
- ❖ Alpha-2 agonists: xylazine abuse; oromucosal dexmedetomidine dog
- ❖ Etorphine: 10000x morphine, 大型動物
- ❖ Ketamine: NMDA; IM
- ❖ Diazepam used in cats
- ❖ 同化性類固醇藥物：
 - ❧ Stanozolol、boldenone 改善動物衰弱的體質
 - ❧ Trenbolone 生長促進劑、皮下植入劑

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感謝聆聽

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