

獸醫藥理學概論

詹東榮

國立臺灣大學獸醫學系

2023

1

聲明事項

本講義僅供參與『112 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。

2

課程大綱

- ❖ 認識動物用藥品
- ❖ 獸醫藥理學課程單元
 - ❖ ACE Inhibitors、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

3

- ❖ 認識動物用藥品
 - ❖ 寵物用藥簡介
 - ❖ 產食動物用藥簡介

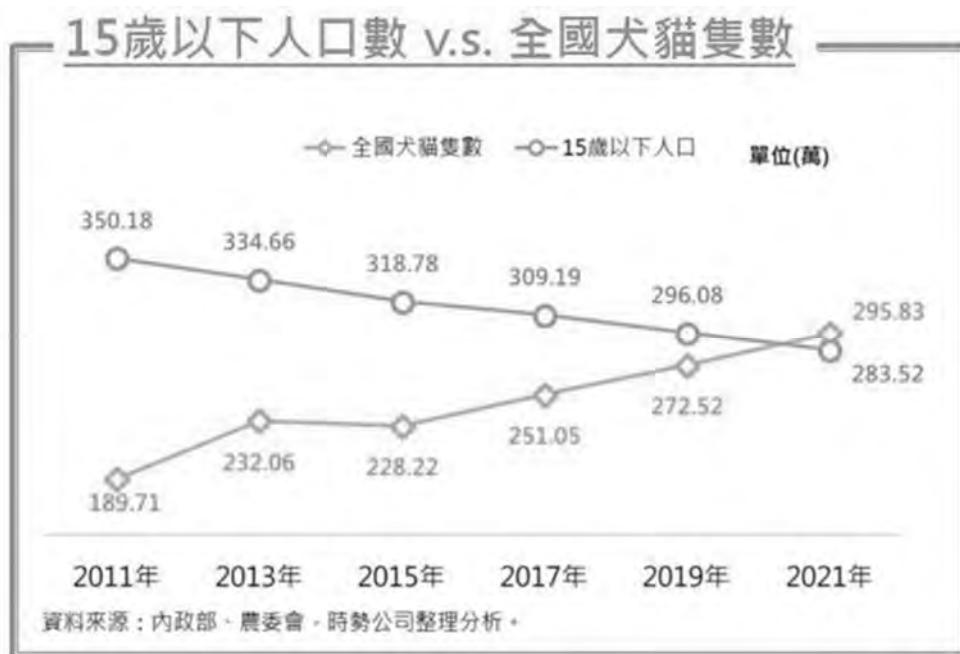
4

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：行政院農業委員會動植物防疫檢疫局、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：豬雞牛羊鴨鵝魚鱉蝦…
 - ❖ 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

5

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>

6

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%



7

寵物用藥之特性(1)

❖ 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……

❖ 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…

8

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

9

產食動物用藥 動物用藥品對禽畜養殖的功用

- ◆ 預防、治療畜禽動物疾病，避免疫情擴大
- ◆ 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)

10

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**
- ❖ 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



11

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

12

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

13

Systemic Pharmacology

- ❖ **自泌素(Autacoid)藥理**
 - ❖ 抗組織胺藥物： H_1 、 H_2 拮抗劑
 - ❖ 非固醇類抗發炎藥物(NSAID)；用藥安全
 - ❖ 血清素致效劑&拮抗劑
 - ❖ 介白素拮抗劑Leukotriene antagonists
 - ❖ 腎素-血管收縮素Renin-angiotensin
 - ❖ 血管收縮素轉化酶抑制劑Angiotensin converting enzyme (ACE) inhibitors
 - ❖ 血管收縮素拮抗劑

14

Renin-Angiotensin System

- ❖ A group of polypeptide autacoids
- ❖ Angiotensinogen (a plasma -globulin)

↓
Renin 腎素
(produced by juxtaglomerular cells)

Angiotensin I

↓ ACE (lung capillary endothelial cells
peptidyl dipeptidase, kininase II)

Angiotensin II (active) 血管收縮素

↓ Angiotensinase

Angiotensin III (inactive)

15

Pharmacological Effects

- ❖ Vasoconstriction: 40X more potent than NE
- ❖ ↑ Synthesis & secretion of aldosterone
- ❖ ↑ Secretion of antidiuretic hormone (ADH)
- ❖ Stimulation of central sympathetic discharge
 - ✉ Positive inotropic & chronotropic effects 強心
- ❖ Cardiac & vascular hypertrophy 心血管肥大
- ❖ Overall effects
 - ✉ ↑ Blood pressure
 - ✉ ↑ Sodium & water retention
 - ✉ Long-term effect (CV remodeling)

16

Angiotensin II Receptors

- ❖ Mediate the effect of angiotensin II
- ❖ Widely distributed
- ❖ AT1: G protein-coupled
 - ❖ Predominately expressed in the cardiovascular system
 - ❖ High losartan affinity
 - ❖ Equal affinity for angiotensin II
 - ❖ Losartan: a drug used to treat hypertension & diabetic nephropathy
- ❖ AT2: low losartan affinity

17

ACE Inhibitors

- ❖ **Captopril, enalapril, lisinopril, benazepril, ramipril, quinipril, fosinopril & imidapril**
- ❖ **Indications**
 - ❖ Antihypertension in both human & animal
 - ❖ Favorable side effect profile
 - ❖ Drug of choice for patients with diabetes, ischemic heart diseases or hypertrophic left ventricles
 - ❖ **1st choice for canine systemic hypertension; also used in cats**

18

ACE Inhibitors

- ❖ **Chronic heart failure: congestive heart failure, dilated cardiomyopathy, hypertrophic cardiomyopathy (HCM)**
- ❖ ↓ **Progression of chronic renal failure in cats (& possibly dogs)**
- ❖ **Slow renal function deterioration & partially mitigate hypertension in cats with renal disease**

19

ACE Inhibitors for Cat & Dog

許可證字號：動物藥入字第06993號

動物用藥品名稱：伏泰康F5

英文名稱：FORTEKOR FLAVOUR 5MG TABLETS

業者名稱：台灣禮藍動保股份有限公司

心衰竭、腎衰竭

效能(適應症)：犬：治療犬心臟衰竭。貓：治療腎衰竭。

成分：EACH TABLET (200.02MG) CONTAINS :
BENAZEPRIL (AS HYDROCHLORIDE)...4.60MG

核發日期：中華民國104年06月02日

20

Angiotensin AT1 Receptor Antagonists

- ❖ **Losartan**
 - ❖ Used to treat hypertension and type II diabetic nephropathy in human
- ❖ **Telmisartan**
 - ❖ Approved as a human & animal drug
 - ❖ Human: hypertension,
↓cardiovascular risk
 - ❖ Cat oral solution: hypertension,
kidney disease (renal failure)

21

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)**

22

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)

23

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

24

Phosphodiesterase V

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



25

High Altitude Illness 高海拔疾病

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

26

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
 - ❖ 積劑、止積劑
 - ❖ 炎症性腸道疾病治療藥物

27

Systemic Pharmacology

- ❖ 內分泌藥理
 - ❖ 腦下垂體
 - ❖ 甲狀腺
 - ❖ 腺臟
 - ❖ 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

28

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

29

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

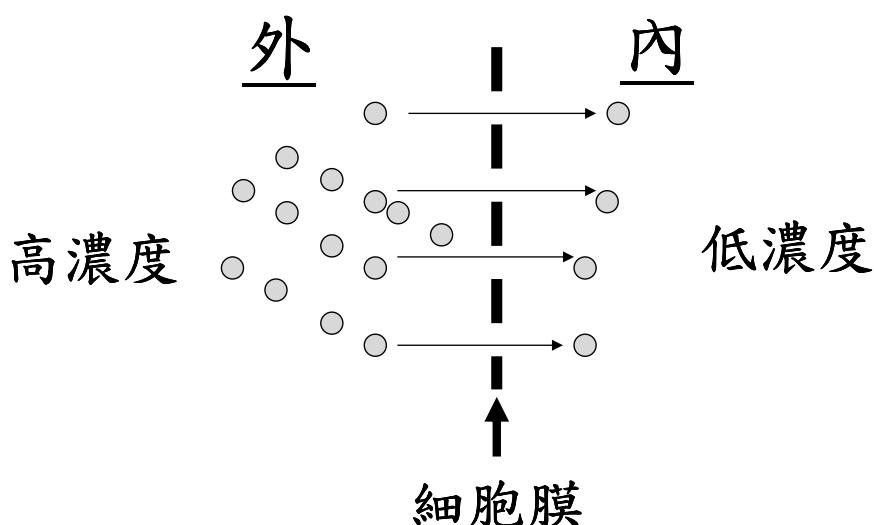
30

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

31

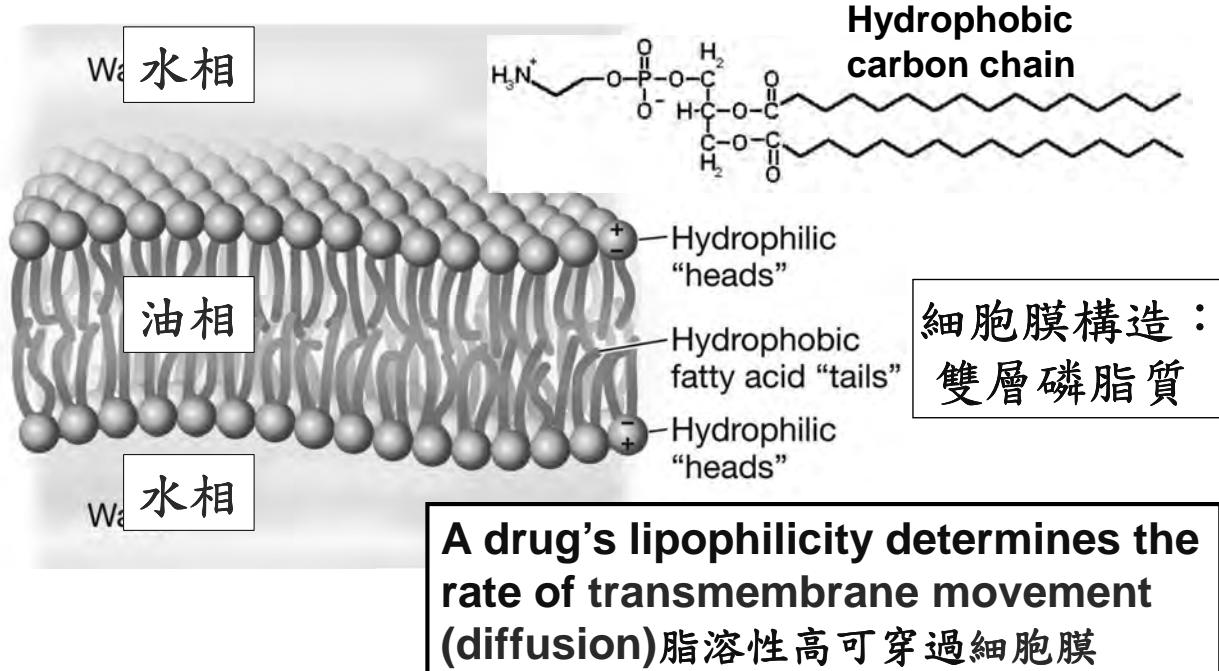
被動擴散(Passive diffusion)



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

32

Phospholipid Bilayer 雙層磷脂質



<https://www.bioexplorer.net/phospholipid-bilayer.html/>

33

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

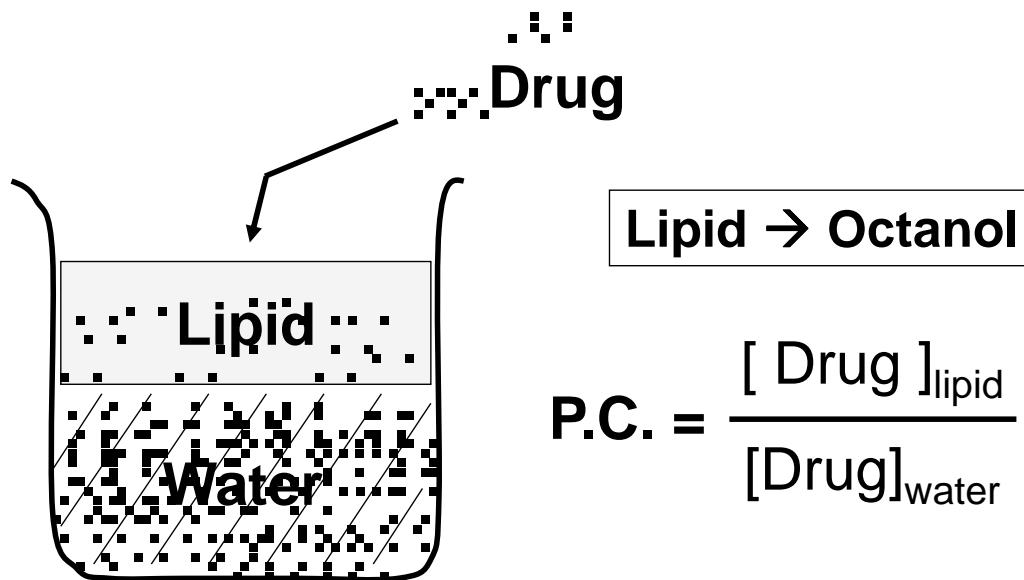
D：擴散係數，是一個常數

A：擴散的面積

K_p：油水分配係數 Why K_p?

34

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



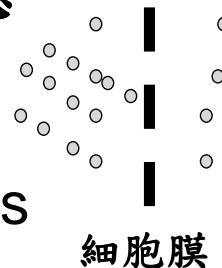
35

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

36

Ion Trapping離子捕捉效應

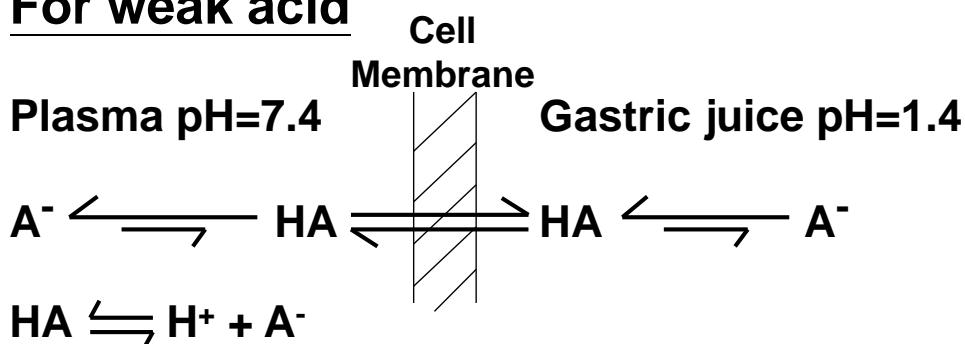


- Different amounts of total drug are found across cell membranes because of a pH gradient
 - More total drug is found on the side where ionization occurs to the greatest extent
 - pH 影響藥物的解離(ionization)程度
 - 解離態(離子化)的藥物無法穿過細胞膜

37

Henderson and Hasselbalch Equation

For weak acid



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

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

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

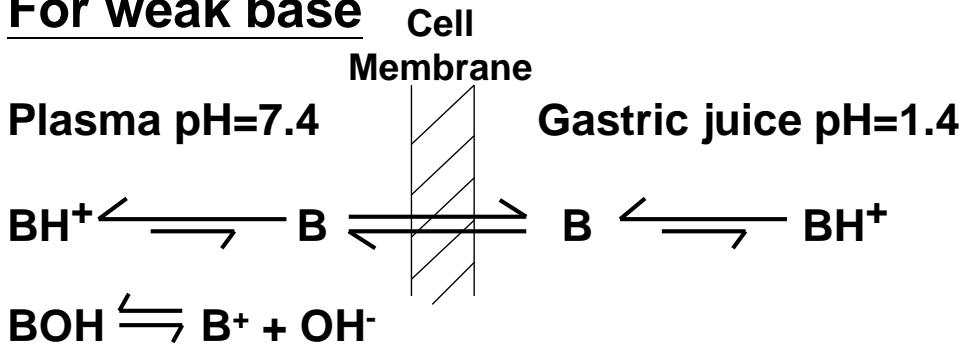
$$-\log[H^+] = -\log k_a + \log \frac{[A^-]}{[HA]}$$

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

38

Handerson and Hasselbalch equation

For weak base



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

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

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

$$\text{pOH} = \text{p}k_b + \log \frac{[\text{B}^+]}{[\text{BOH}]}$$

$$\text{pH} = 14 - \text{pOH} = 14 - \text{p}k_b - \log \frac{[\text{B}^+]}{[\text{BOH}]} = \text{p}k_a - \log \frac{[\text{B}^+]}{[\text{BOH}]}$$

39

Learning Question

What is the percentage of ionized form of 阿斯匹林 aspirin ($\text{p}K_a = 3.4$) in plasma ($\text{pH} = 7.4$) ?

$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

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

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

Therefore, 99.99% of aspirin is ionized form.

弱酸性藥物在血液和胃液之間的分布比率

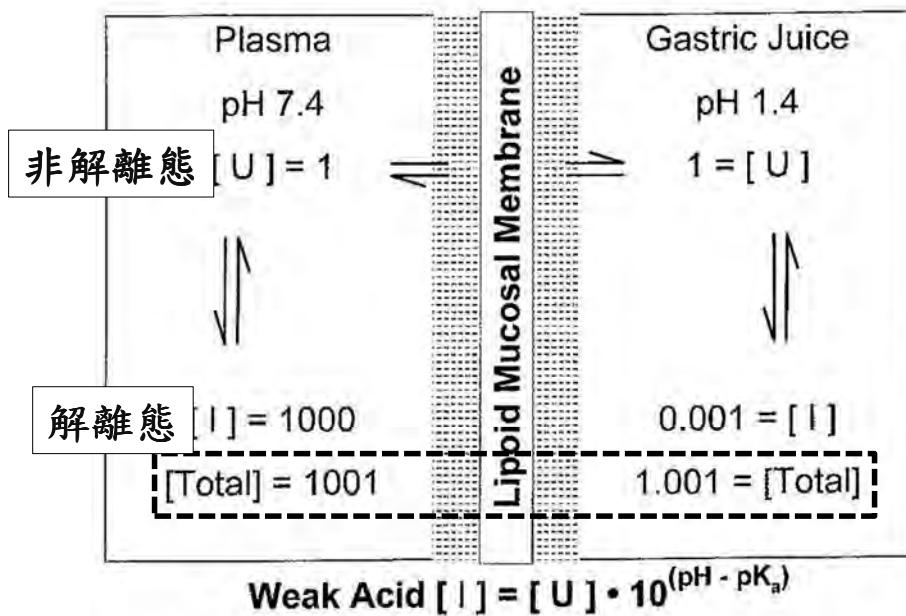


FIG. 3.2—Effect of pH gradient on distribution of a weak organic acid (pK_a 4.4) between blood plasma (pH 7.4) and gastric juice (pH 1.4). In this figure, $[I]$ and $[U]$ represent the concentrations of the ionized and nonionized fractions of the drug, respectively. A dynamic equilibrium exists between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

41

Ion Trapping離子捕捉效應

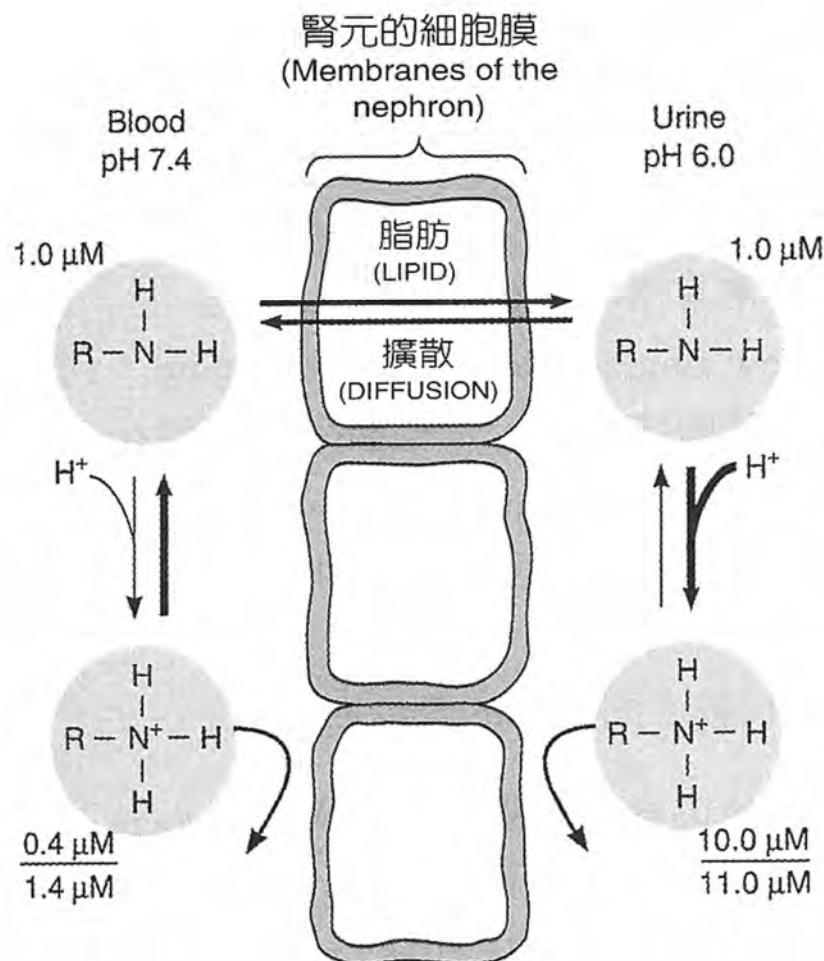
- Kidney 腎臟
 - Nearly all drugs filtered at the glomerulus
 - Most drugs in a lipid-soluble form will be absorbed by passive diffusion
 - To increase excretion:
 - Change the urinary pH to favor the charged (ionized) form of the drug
 - 1. Weak acids: excreted faster in alkaline pH (anion form favored)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

42

尿液比血液更酸時，加速腎臟排除

43

弱鹼性藥物從腎臟排除



	<u>pH 6.8</u> (酸性)		<u>pH 7.4</u> (鹼性)	
	(非解離態可通過細胞膜)			
	解離 [I]	非解離 [U]	II	非解離 [U] 解離 [I]
酸性藥物	低	高	II	低 高
	0.5	1	II	1 2
Total	1.5		II	3
酸性藥物的濃度	血液為低			

44

pH 6.8 (酸性)		(非解離態可通過細胞膜)		血液 pH 7.4 (鹼性)	
解離	非解離	II	非解離	解離	
[I]	[U]	II	[U]	[I]	
鹼性藥物	高	低	II	高	低
		II			
	2	1	II	1	0.5
Total	3	II		1.5	
鹼性藥物的濃度血液為高					

45

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

Drug	：血之藥物濃度比值		Concentration ratio (milk ultrafiltrate:plasma ultrafiltrate)	
	高比值代表	藥物	高	
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

- 弱酸性抗生素不進入。
- 除 kanamycin (高性) 進入，其他弱鹼性抗生素容血液進入。

46

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

47

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

48

Tranquilizer Nomenclature

- ❖ Major tranquilizers = Neuroleptic drugs
= Neuroleptics = Antipsychotics =
Antischizophrenics
 - ❖ Phenthiazines
 - ❖ Butyrophanones
 - ❖ Thioxanthenes
- + **α_2 -Adrenergic agonists**
- ❖ Minor tranquilizers
 - ❖ Benzodiazepines

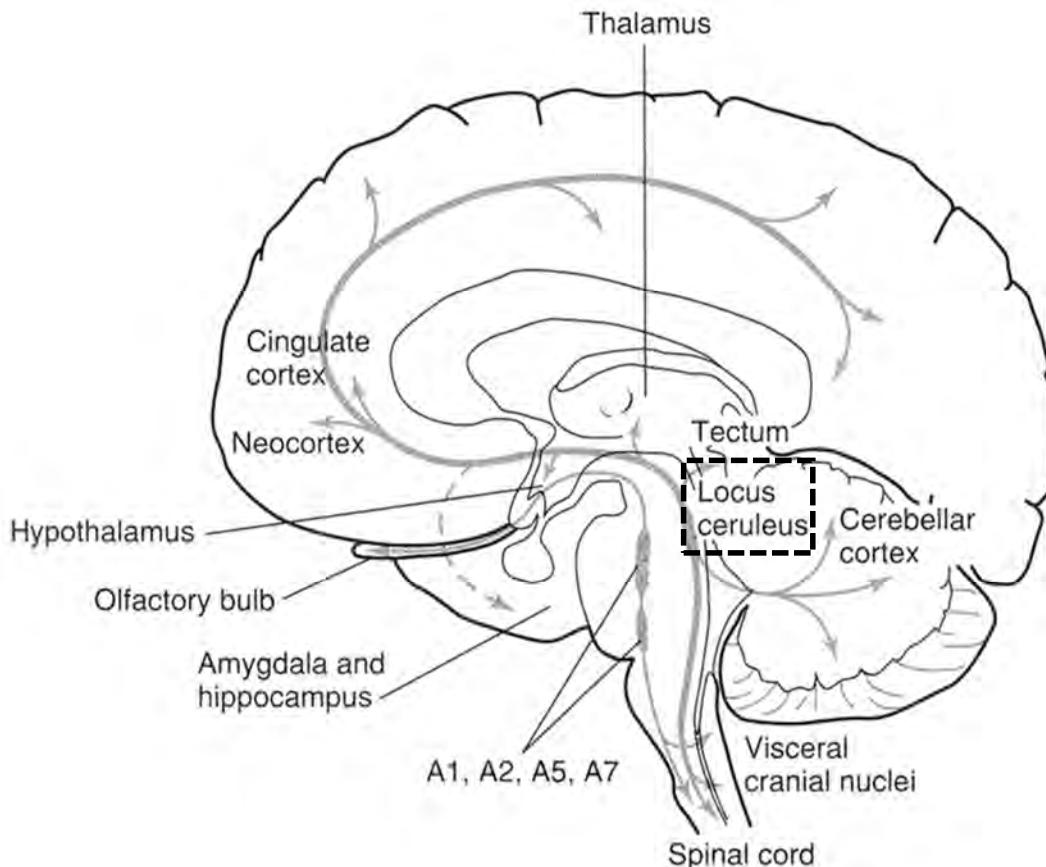
49

Drugs Used in General Anesthesia

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

50

Only a few thousand neurons in the brain make NE



51

Norepinephrine (NE) in the Brain

- Cell bodies of NE neurons are located in brainstem (locus ceruleus & medulla)

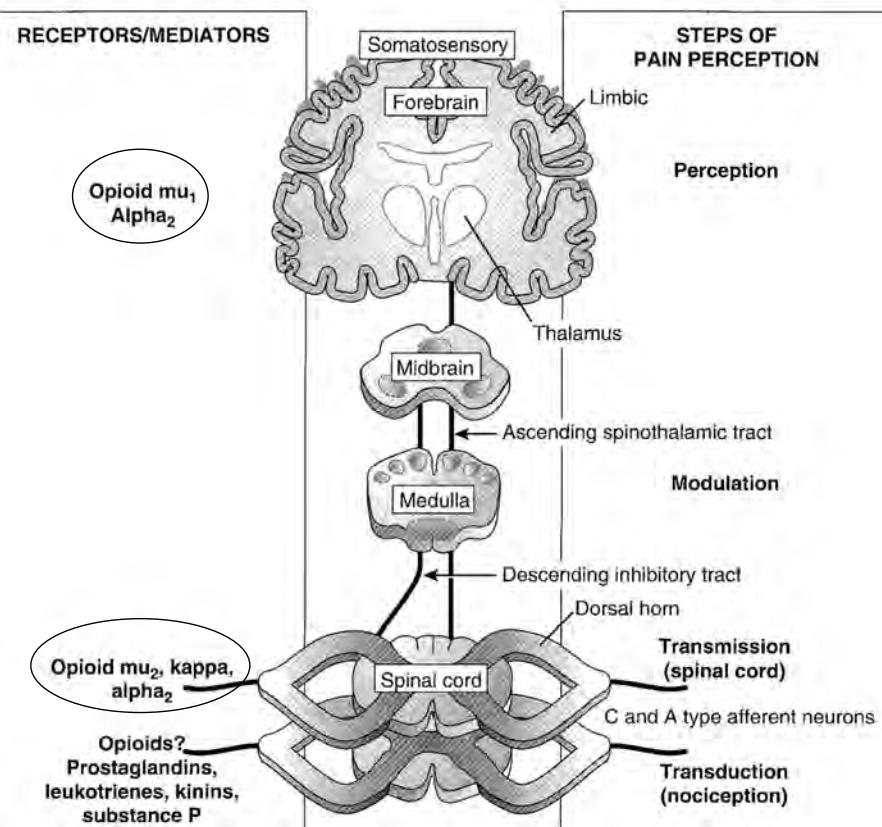
1. Axons project widely throughout the brain

- 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

52

Pain Pathways & Receptors



53

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

54

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

55

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

56

α_2 -Adrenergic Agonists

- **Cardiopulmonary effects**
 - ❖ **Bradycardia**
 - ❖ **Negative inotropic effect: decrease cardiac output**
 - ❖ **Xylazine biphasic effect on blood pressure:** transient initial hypertension (peripheral 1 & 2 effect) followed by prolonged hypotension (central 2 effect)
 - ❖ **Mild respiratory depression alone**

57

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)***

58

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)**

59

Xylazine

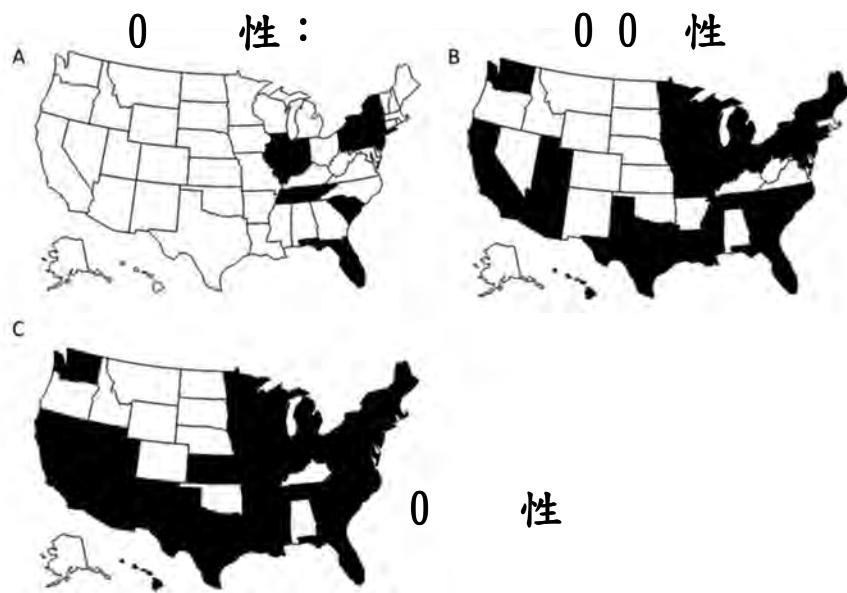
- ❖ **Used in dogs, cats, horses, ruminants, avian & exotic species**
- ❖ **Potent analgesic activity**
 - ❧ Acting on α_2 -adrenergic receptors, not opioid receptors
 - ❧ Not antagonized by naloxone
- ❖ **Ruminants (cattle) are very sensitive; dose is 1/10 of dogs, cats and horses**
- ❖ **Synergism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

60

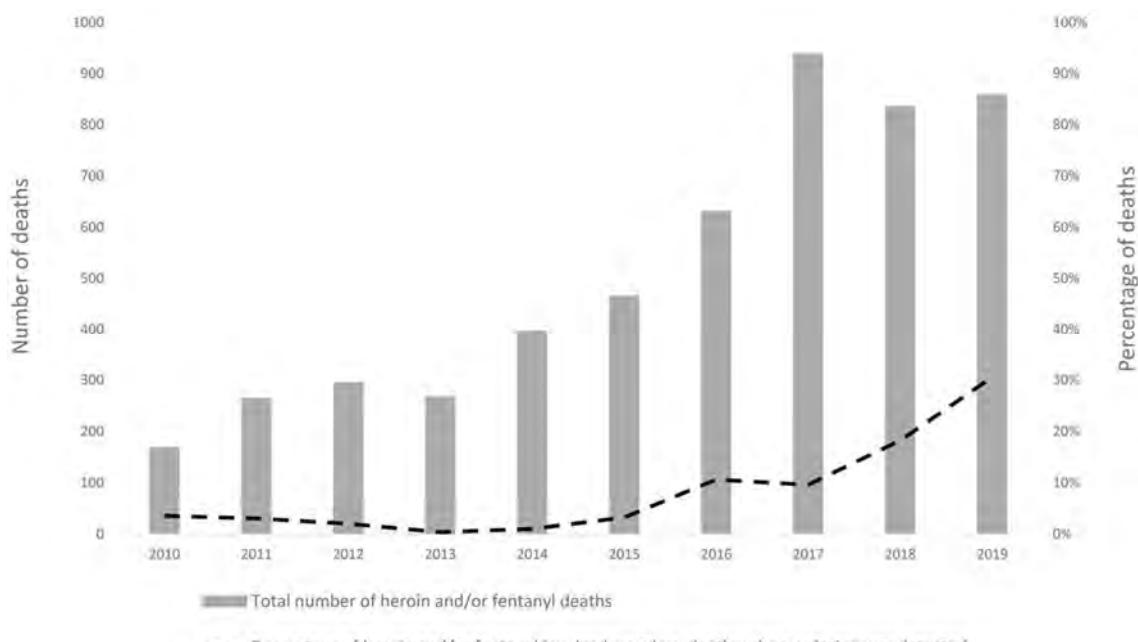
Xylazine – 全 興 用 藥 物

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

❖ 性 上



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



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



- 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



63

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，提供其抑制、鎮靜與止痛的效果。此外，可作為犬與全麻醉的預用藥。

64

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

65

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

在加護病房治療期間，受管及人呼吸護病人之鎮靜作用、非管病人受手術或其他程及或手術或程進行中之鎮靜作用，無論上何種情況，靜脈注射與的間，不得過一小時。

註銷狀態
註銷理由
有效日期
許可證種類
舊證字號
相關審查文件編號
中文品名
英文品名
國應症
劑型
標籤・仿單及包裝加註
藥品類別
藥品分類
主要成份略號
說明書內容

05限由醫師使用
管制藥品分類級別
監視期限
DEXMEDETOMIDINE HYDROCHLORIDE

上午 11:19
2020/3/13

66

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

67

K他：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

- ❖ 用於犬、貓、兔、羊、牛、
豬、馬、禽類和魚類……
- ❖ 魚肌肉注射

68

Ketamine之效

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。

種非經濟動物之麻醉； 、保定及 間之鎮靜

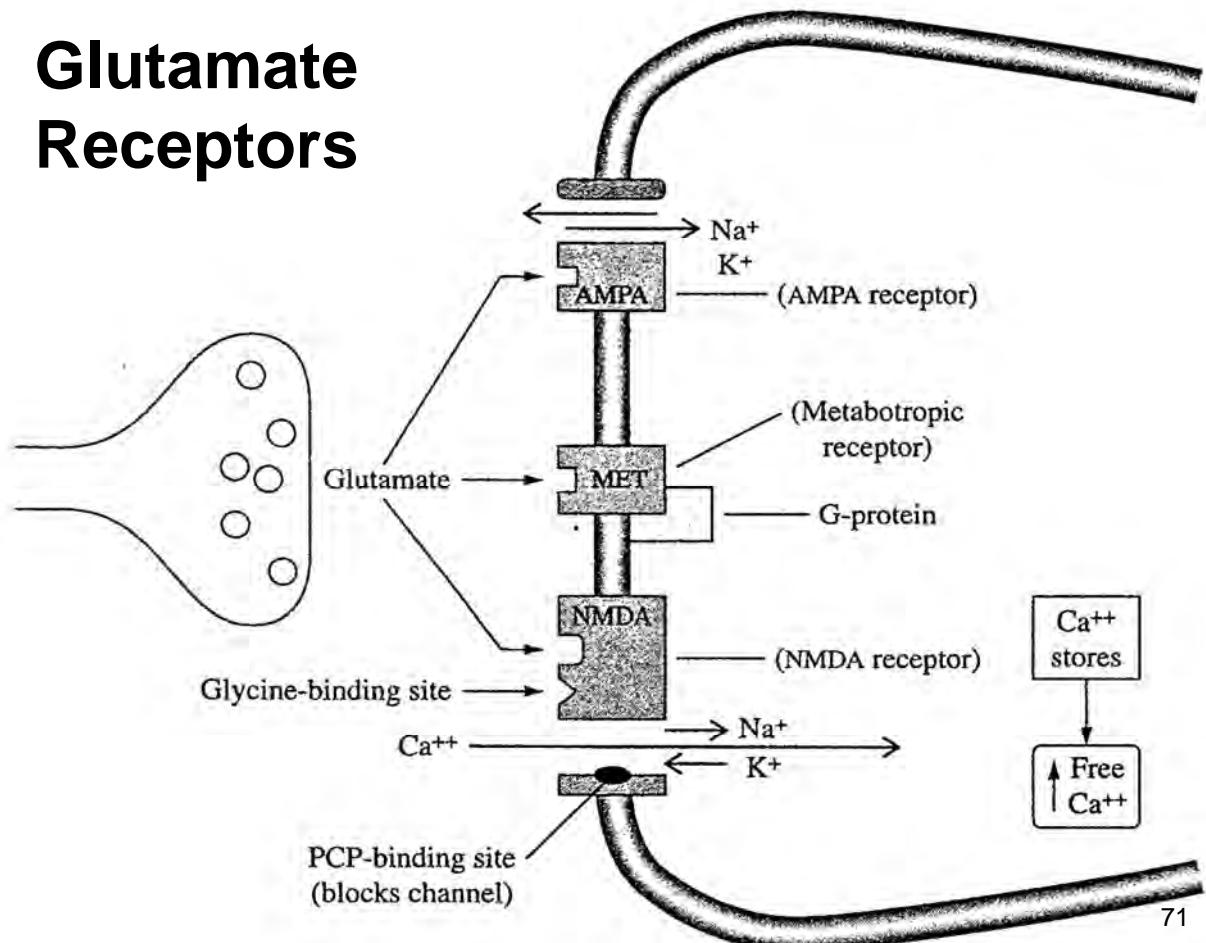
69

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

70

Glutamate Receptors

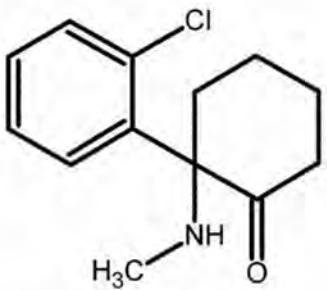


71

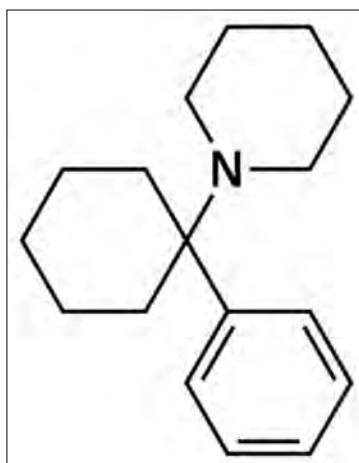
Glutamate Receptors

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

72



Ketamine



Tiletamine

Phencyclidine

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

73

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**

74

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

75

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

76

Ketamine Preanesthetic Medication

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

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**

Fentanyl and Derivatives

- ❖ **Fentanyl: human & animal drug**
 - ❖ Potency 100x of morphine
 - ❖ Analgesia: 2-50 µg/kg in human
 - ❖ Transdermal patch: 25 µg/h
- ❖ **Sufentanil: human & animal drug**
 - ❖ Potency 5-10x of fentanyl
 - ❖ Analgesia: 0.5-5 µg/kg in human
 - ❖ Parenteral: IV, IM, SC, epidural
- ❖ **Carfentanil: animal drug only**
 - ❖ Potency: 100x of fentanyl
 - ❖ Used in large wild animals

79

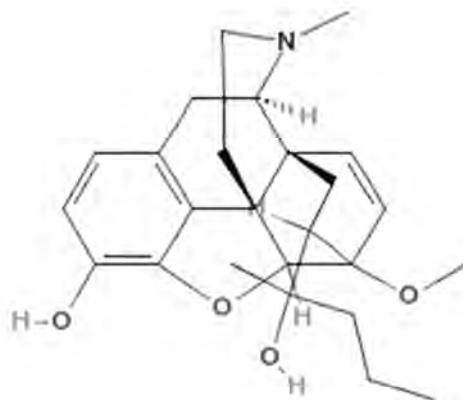
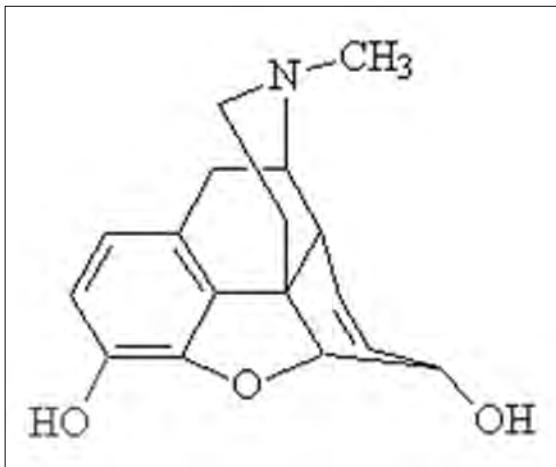
Etorphine (M99[®])

- ❖ **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**

80

Morphine

Etorphine

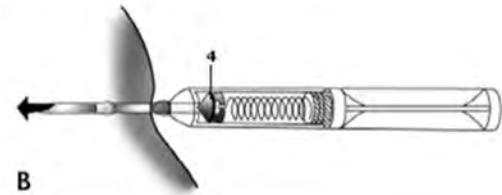
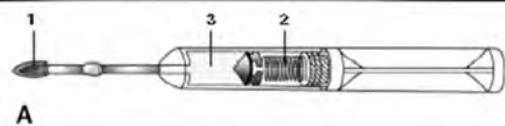


www.ChemDrug.com

81

Drugs for Use in Tranquilizer Dart

- ❖ **Injectable anesthetics**
 - ❖ Ketamine, thiopental
- ❖ α_2 -adrenergic agonists
 - ❖ Detomidine, xylazine
- ❖ **Opioids**
 - ❖ Carfentanil, etorphine
- ❖ **Major tranquilizers**
 - ❖ Acepromazine, azaperone, haloperidol



82

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

83

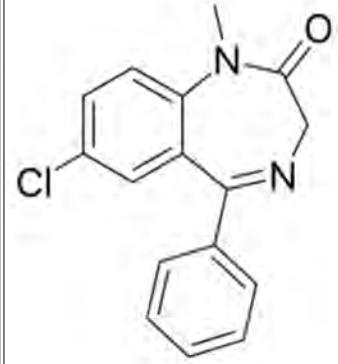
Drugs Used to Modify Behavior

- ❖ **Major tranquilizers & α_2 -adrenergic antagonists**
- ❖ **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

84

Minor tranquilizer: Benzodiazepines

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



Diazepam

85

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

86

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 by FDA, but can be used by veterinarians as extra (off)-label drugs
 - ❖ Use drugs not in accordance with the approved label directions

87

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)

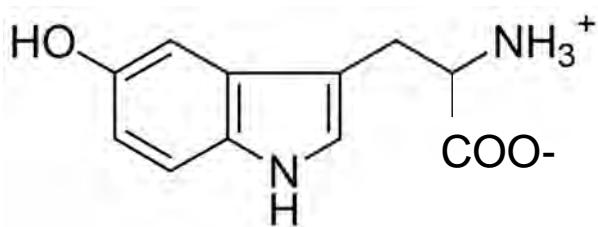
88

Antidepressants

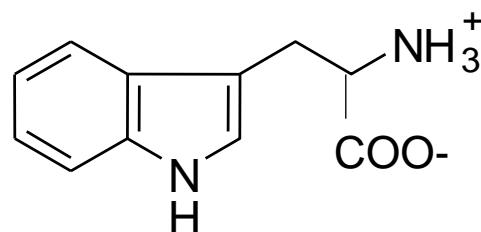
- ◆ Tricyclic antidepressants (TCA)
- ◆ Selective serotonin reuptake inhibitors (SSRI)

89

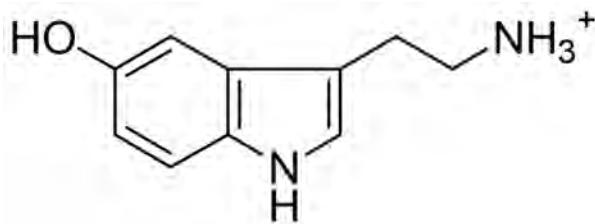
5-HT



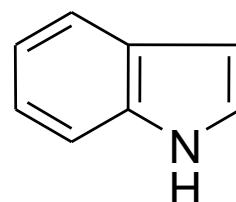
5-hydroxytryptophan



Tryptophan



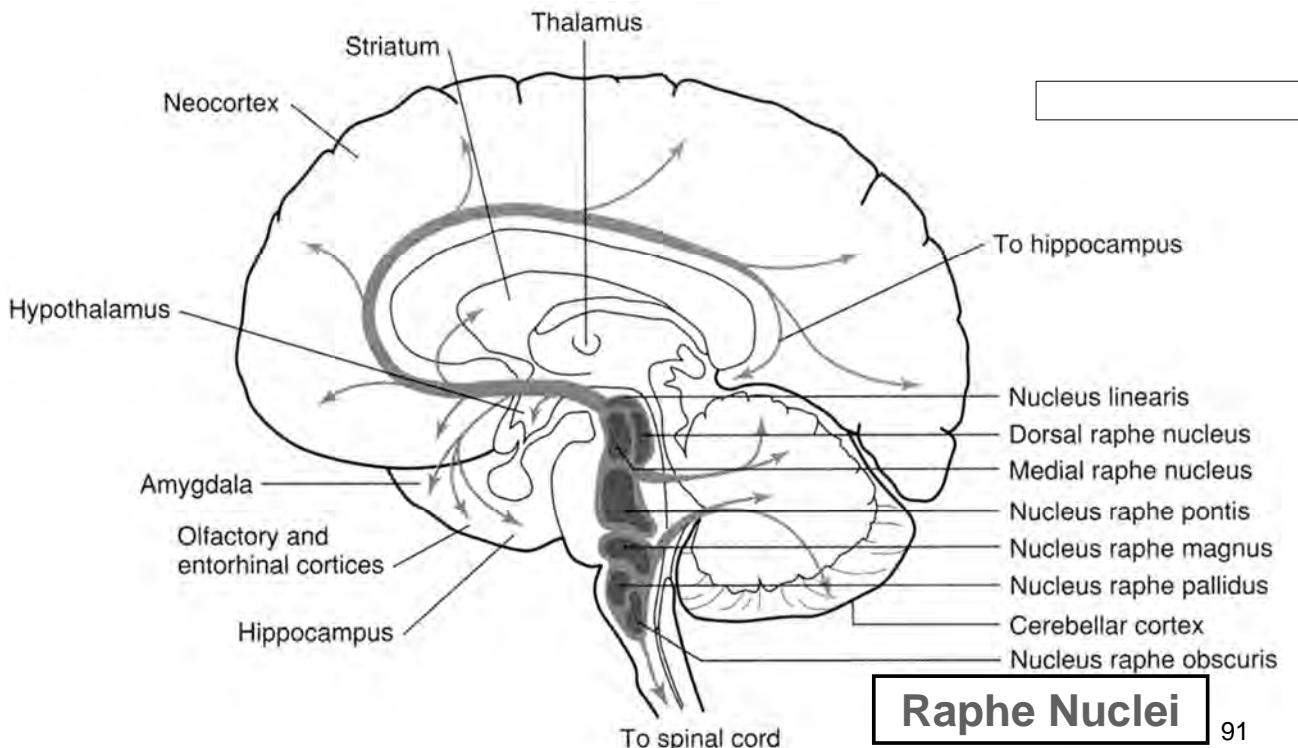
5-hydroxytryptamin
(5-HT)



Indole

90

Serotonin Projection to Many Higher Brain Regions



Raphe Nuclei

91

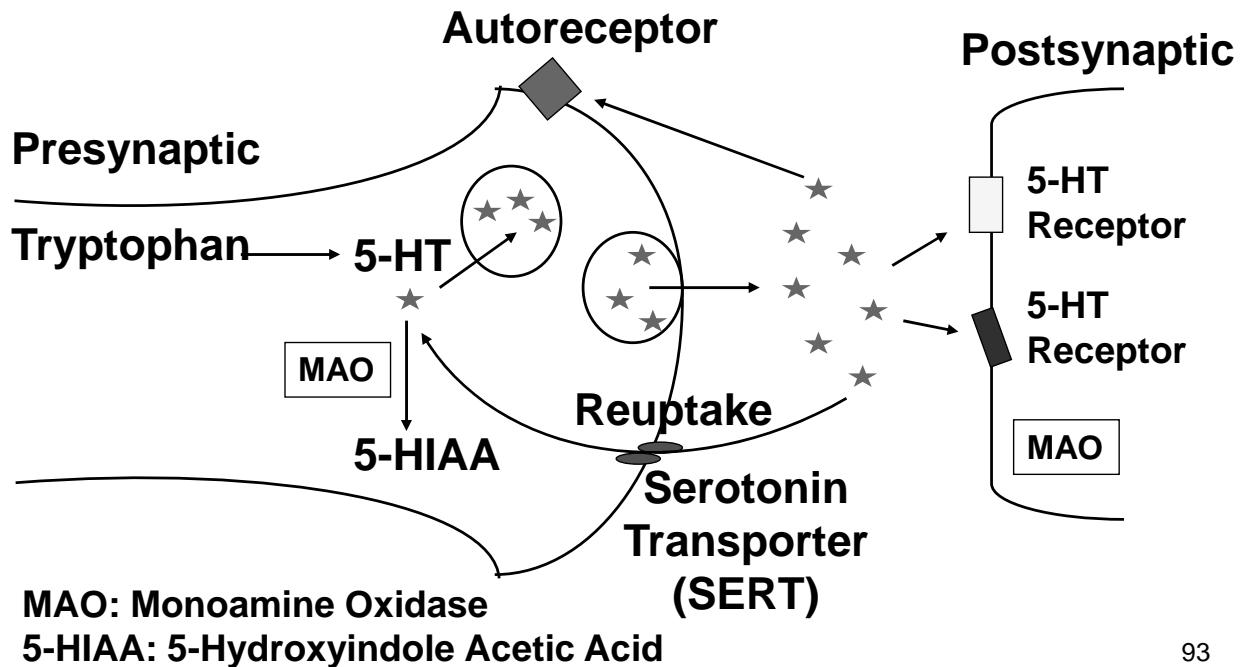
Overview of 5-HT Neurotransmission

- **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

92

5-HT Synapse

- **5-HT Turnover:**



93

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

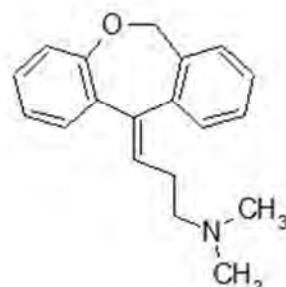
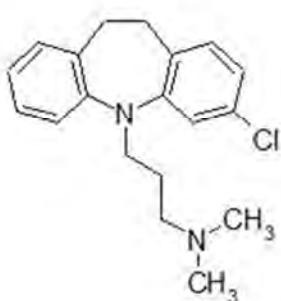
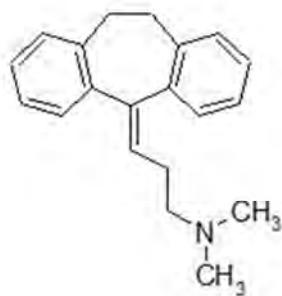
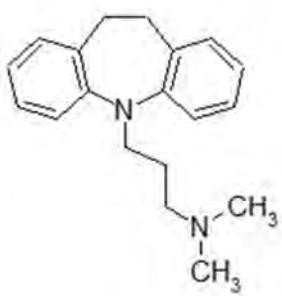
94

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

95

Tricyclic Antidepressants



Imipramine clomipramine amitriptyline doxepin

96

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**

97

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**

98

Noise Aversion (Phobia) in Dogs

- ❖ 症 : Affects one-third of dogs in the U.S.
- ❖ Patients experience fear and anxiety
 - ❖ 對 的 和焦慮反應
 - ❖ Similar to a panic attack in humans
- ❖ Therapeutic drugs
 - ❖ Benzodiazepines (alprazolam, diazepam),
 - ❖ SSRI (fluoxetine 憂解)
 - ❖ Clomipramine 抗憂鬱劑
 - ❖ Dexmedetomidine (oromucosal gel 口 黏膜凝)
 - ❖ An α_2 -agonist

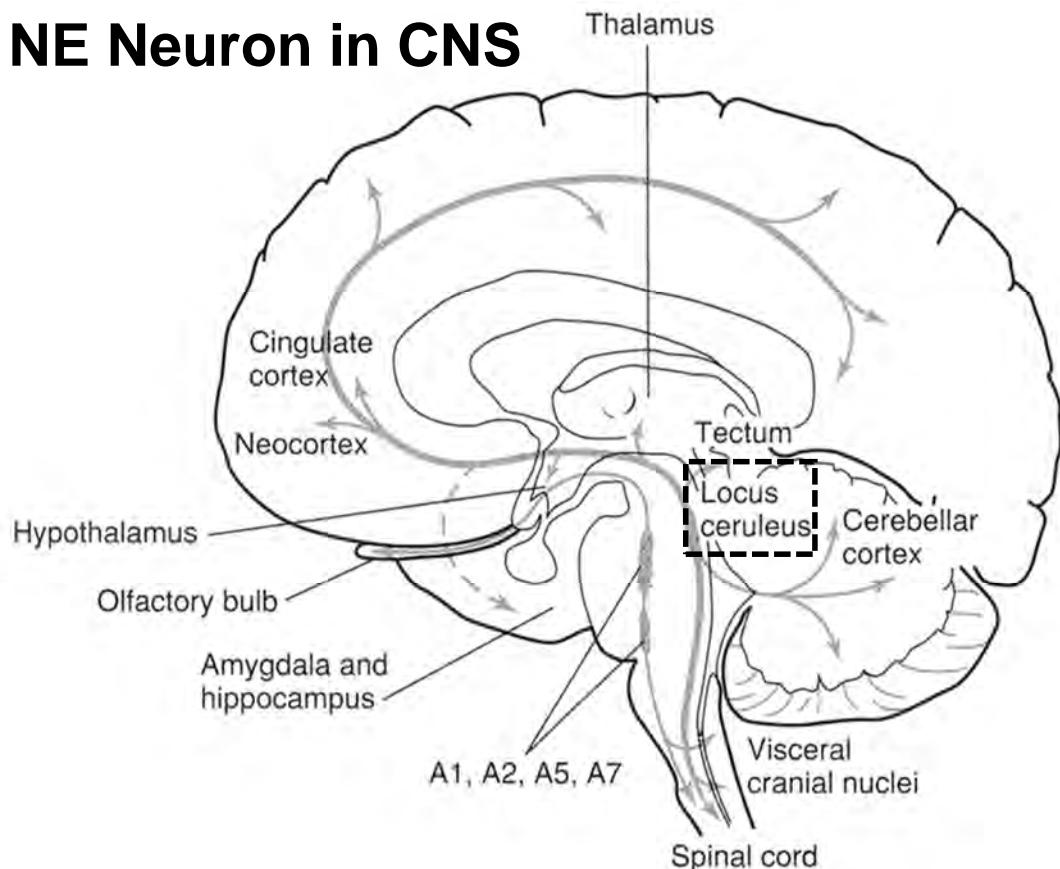
99

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

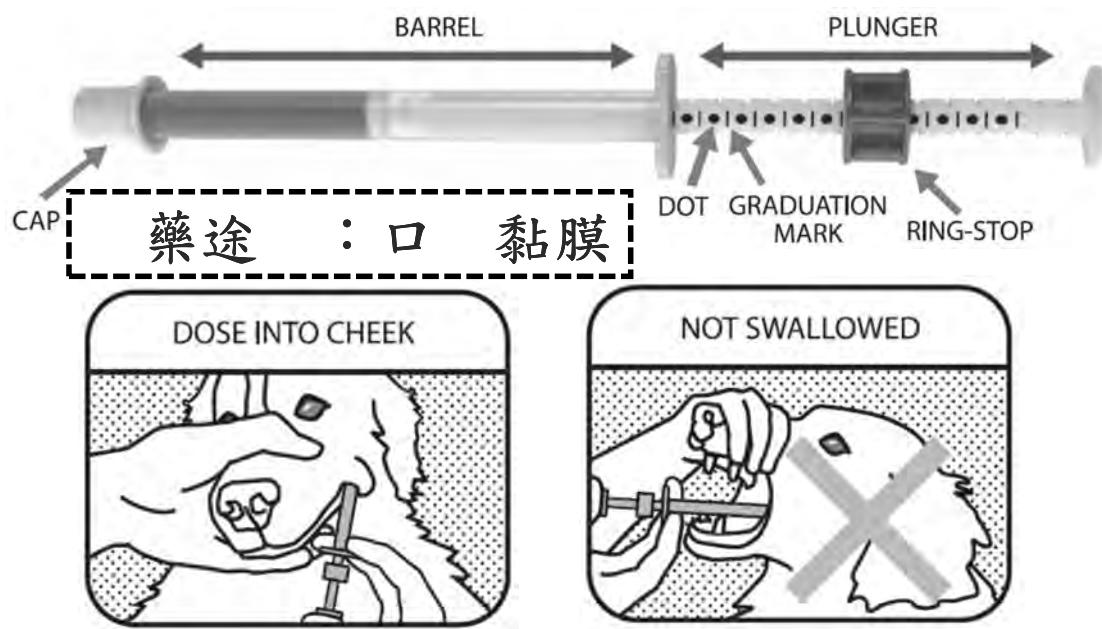
100

NE Neuron in CNS



101

Dexmedetomidine Oromucosal Gel Syringe



102

產食動物之內分泌藥理

103

Endocrine Pancreas

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

104

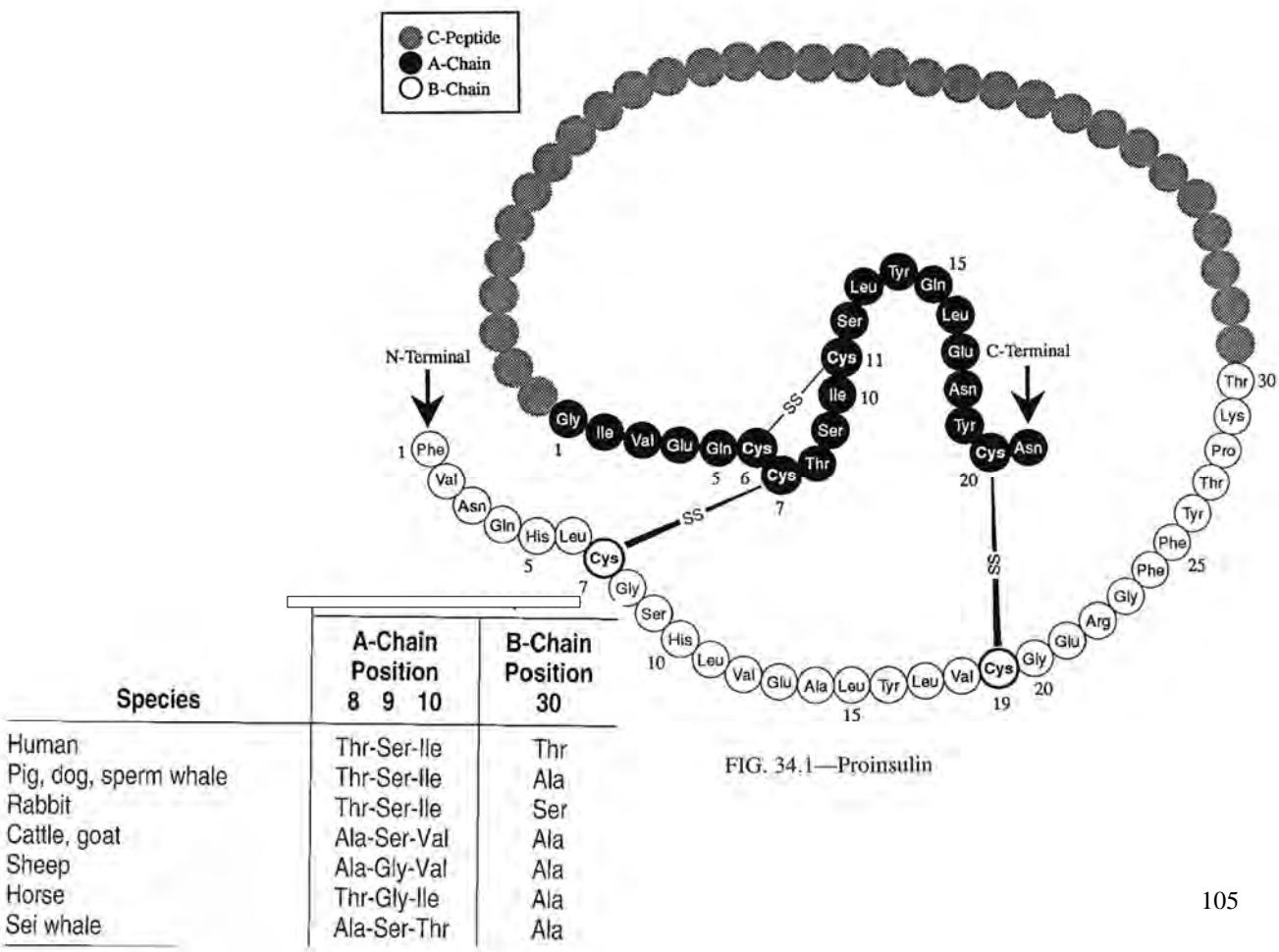


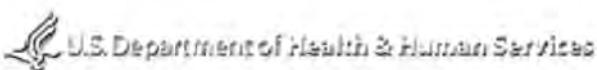
FIG. 34.1—Proinsulin

105

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

106



FDA Center for Veterinary Med

[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

107

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

108

Use of Insulin in Dairy Cows

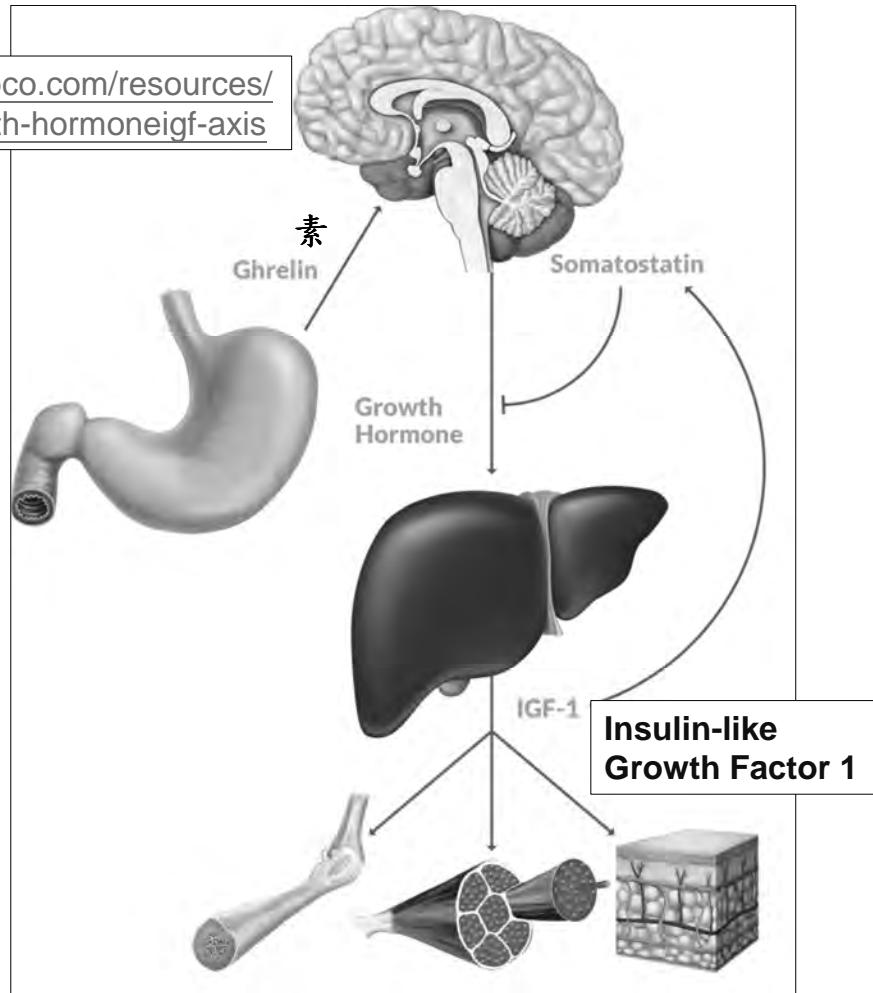
- ❖ Ketosis in cattle
 - ❖ Occurs within the 1st week of lactation due to a negative energy balance
 - ❖ Excessive metabolism of lipid
 - ❖ Some are nonresponsive to glucose or glucocorticoid therapy
 - ❖ Insulin is an effective antiketogenic drug
 - ❖ An adjunct treatment in ketosis therapy
 - ❖ 200-300 IU protamine zinc insulin per cow

109

Anti-insulin Hormones

- ❖ Increase the level of blood glucose
 - ❖ Glucagon
 - ❖ Epinephrine
 - ❖ Growth hormone
 - ❖ Glucocorticoids

110



111

Uses of GH in Animals

- **Increases milk production in dairy cows**
 - **Somotribove**, 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

112

Estrogens

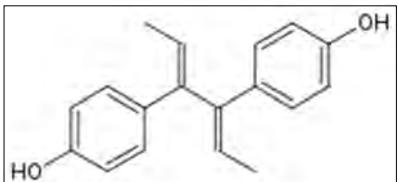
- ❖ Many substances have estrogenic activity
 - ❖ **Steroidal estrogens:** animal sources
 - ❖ Estradiol (estradiol-17^o, E₂)
 - ❖ Estrone (E₁) & Estriol (E₃)
 - ❖ **Nonsteroidal estrogens:** synthetic
- ❖ Stimulate & maintain the reproductive system & the mammary gland
- ❖ Induce estrus
- ❖ Antagonize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

113

Synthetic Estrogens

- ❖ Chemical modifications of natural estrogens
 - ❖ Affect PK, increase duration of action
- ❖ Esters of estradiol
 - ❖ 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

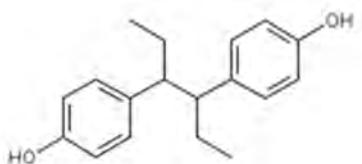
114



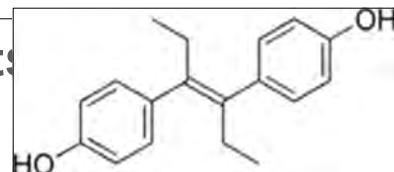
Synthetic Estrogens

- ❖ Nonsteroidal estrogenic agents:

- ❖ Dienestrol



- ❖ Hexestrol

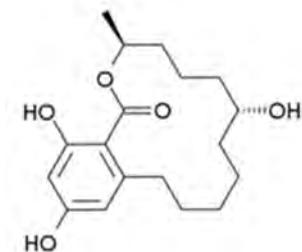


DES

- ❖ Increased risk of endometrial cancer in postmenopausal women

- ❖ Zeranol

- ❖ A mycotoxin (mycoestrogen)



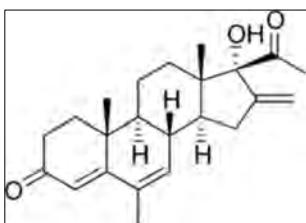
- ❖ Anabolic agent: used as a growth promoter in livestock

115

Progestins

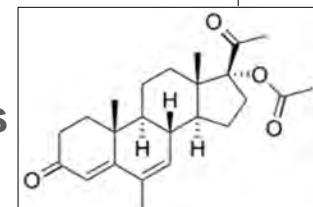
- ❖ Progestins = progesterone + synthetic analogs
- ❖ Inhibit estrus & extend the luteal phase
- ❖ Estrus appears several days a/f the last dose
 - ❖ Synchrony in large animals (estrus cycle control)
 - ❖ Mediated by ↑ gonadotropin secretion
- ❖ Prevent uterine contraction during pregnancy
- ❖ Exhibit anabolic effect due to increased appetite & decreased physical activity

116



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



117

Anabolic Agents

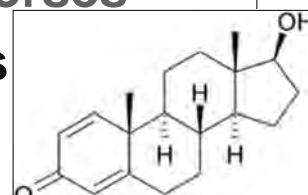
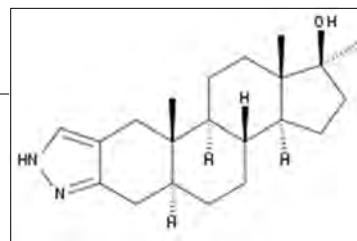
- ❖ **Estrogens**
 - ❖ Estradiol esters, zeranol implants
- ❖ **Progestins**
 - ❖ Progesterone implants
 - ❖ Melengestrol as a feed additive
- ❖ **Androgens**
 - ❖ Testosterone propionate implants
 - ❖ Synthetic anabolic steroids
 - ❖ Stanozolol, boldenone, trenbolone

118

Anabolic Androgens

❖ 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 (+ estradiol) Implants
 - ❖ Growth promoters for cattles



119



感 謝

詹東榮

02-33661287

tonyjan@ntu.edu.tw