*VI LSD No. 239 (§ 102a)
Str No. 109 (§ 304b)
Quinidine (§ 316a)
Procaine amide (§ 316g)
Chlorpromazine (§ 97a)
Reserpine (§ 203a)

B 188.4 central cardiac effects
Z 22 injection into
M 1.1 ventricle
M 500 effect on
M 377 psyche
M 341 behaviour
B 240 ECG

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Pharmacological effects from drugs injected intracerebrally in unanesthetized animals.
J.Amer.Pharmaceut.Ass.(Sc.Ed.)45, 604 (1956).

PROBLEM: Effect of drugs given intracerebrally (i.c.) in nonanaesthetized dogs.
METHOD: Cannula implanted in 3rd cerebral ventricle. Injection varied in volume from 0.2 to 1.0 ml. Intravenous injections within comparable dosage ranges made via the anterior subcutaneous vein of the fore-leg.
DOSAGE: See results
RESULTS:
I. Cardiac glycosides: I.c. injection of 3.2 to 4.4 µg/kg tryptamine-strophanthidin (T-S) or 6.4 to 8.4 µg/kg Str produced bradycardia and ST depression in the ECG. Secondary effects were: salivation, defecation, mydriasis, shivering, generalized tremor and pallor of mucous membranes and retina. These effects disappeared after 11 minutes. With larger doses (10.9 to 17.2 µg/kg T-S or 31.4 to 57.4 µg/kg Str) ventricular extrasystoles and paroxysmal ventricular tachycardia occurred after 3 minutes. After 2 to 9 minutes some animals had bigeminy, trigeminy, sinus tachycardia, multifocal ventricular tachycardia and periodic P-wave suppression. Death was due to respiratory paralysis and ventricular fibrillation. Additional secondary effects were: barking, generalized excitement, lateral and vertical nystagmus, opisthotonos, tense abdominal musculature, retching, emesis, micturition, tachypnoea and orbicularis muscle twitching. These effects must be centrally induced, because 8.9 to 9.8 µg/kg of T-S or 31 µg/kg Str i.v. had no effect. 20.1 to 26.8 µg/kg T-S produced a deep Q-wave and a biphasic or inverted T-wave with a late sagging ST segment and bradycardia. These effects lasted only 10 minutes. 77 µg/kg

Str produced only bradycardia lasting 9 minutes and no secondary effects. Injection of the vehicles into the 3rd ventricle had no effect. 15 to 37.3 mg/kg of hexamethonium chloride completely abolished the secondary effects and re-established normal cardiac rhythm within 8 minutes. 20 mg/kg chlorpromazine was also effective. Pentobarbital anaesthesia decreased cardiac rate and induced regular sinus rhythm.

2. Quinidine sulfate: 0.45 to 4.0 mg/kg i.c. produced paroxysmal ventricular tachycardia, alternating nodal extrasystoles or auricular tachycardia followed by a diminishing sinus tachycardia. Immediate secondary effects were: retching, micturition, defecation, mydriasis, nystagmus, respiratory depression, mucous membrane pallor and Stage III, Plane II general anaesthesia with corneal reflexes still present. These effects were not seen after 2.8 to 8.1 mg/kg i.v. 0.5 ml propylene glycol (20% of the vehicle) i.c. had no such effects. Quinidine caused no deaths.

3. Procaine amide: 5.2 to 7.1 mg/kg i.c. had little or no effect on the ECG. Secondary effects were: defecation, nystagmus, slight twitching of facial musculature and Stage III, Plane II anaesthesia. 10.3 mg/kg i.v. had none of these effects.

4. Chlorpromazine: 0.3 mg/kg i.c. tranquillized the animal for 16 minutes and produced a lowered, biphasic T-wave and no other effects. 0.93 to 1.1 mg/kg caused bradycardia, inverted, lowered or biphasic T-wave, followed by tachycardia, series of 1, 2 or 3 ventricular extrasystoles and coupled normal beats. After 20 minutes T-wave became upright. Secondary effects were: analgesia, tranquillization, shivering, decreased respiratory rate, defecation, mydriasis and occasional barking. Body temperature fell by 0.3° to 1.6° over a period of 35 minutes and then returned to normal 15 minutes later. Animals apparently normal 10 to 12 hours hours later. 20 mg/kg i.v. produced variability in the height of the T-wave with tachycardia followed by bradycardia. ECG was normal 11 to 20 minutes later. Secondary effects were: attempted emesis, defecation, vertical and lateral nystagmus, miosis with reactive pupils, ataxia, micturition and analgesia with no reaction to painful stimuli. Body temperature decreased by 0.6°. Respiration was slightly depressed.

5. Reserpine: 2.2 to 4.5 μg/kg i.c. produced salivation, retching and emesis. No other effects. Animals normal after 20 minutes. 25 μg/kg caused salivation, repeated emesis, slight miosis and defecation. ECG changes were tachycardia, biphasic or inverted T-wave and accentuated P-wave. Animals normal within 24 hours.

6. LSD: 1.6 to 10 μg/kg i.c. produced within 1 to 3 minutes

whining, head-shaking, salivation, retching, emesis, micturition, tachypnoea and ataxia. After 6 minutes, mydriasis with reactive pupils. Recovery after 15 to 20 minutes, but throughout this period the animals appeared frightened. The animals barked for several hours after the other effects of LSD had disappeared. The animals reverted from an adult behaviour to a puppy one, but there was no impairment of their ability to obey commands or perform simple tasks. This personality change was the most striking effect.

7. Analysis of effects:

TABLE I.—COMMON EFFECTS FROM INTRACEREBRAL INJECTION OF DRUGS

Effect	Strophanthin-K and Tryptamine Strophanthidin	Procain-amide	Quini-dine Sulfate	Chlor-proma-zine	Reser-pine	LSD-25	Possible Sites of Action
Salivation	+	+	−	−	+	+	Pre-optic hypothalamus
Retching	++	−	+	−	++	++	Brain stem reticular formation
Emesis	++	−	−	−	++	++	Chemoreceptor trigger zone
Mydriasis	++	−	++	+	−	++	Posterior hypothalamus
Nystagmus	+	+	+	−	−	−	Pontine area or medial longitudinal fasciculus
Defecation	+	+	+	+	+	−	Hypothalamic, pre-optic and supra-optic nuclear areas
Micturition	++	−	++	−	−	+	Pre-optic hypothalamus
Vasoconstriction	++	−	+	−	−	−	Posterior hypothalamus, vasomotor center in medulla
Shivering	++	−	−	+	−	−	Posterior hypothalamus
Tachypnea	++	−	−	−	−	+	Respiratory center in medulla
Bradypnea	−	−	−	+	+	−	Respiratory center in medulla

+ Present; − absent.

TABLE II.—UNCOMMON EFFECTS FROM INTRACEREBRAL INJECTION OF DRUGS

Drug	Effect	Possible Site of Action
Strophanthin-K and tryptamine-strophanthidin	Abnormal electrocardiogram ending in ventricular fibrillation. Generalized excitation	Anterior and posterior hypothalamus
Procainamide	Stage III, Plane II general anesthesia with corneal reflexes present	Ascending reticular system; hypothalamus
Quinidine sulfate	Stage III, Plane II general anesthesia with corneal reflexes present	Ascending reticular system; hypothalamus
Chlorpromazine	Analgesia and tranquilization. Hypothermia, bradycardia followed by tachycardia	Hypothalamus and brain stem, thermoregulator center, posterior and anterior hypothalamus
Reserpine	Miosis	Optic chiasma, optic tract, pretectal region
LSD-25	Ataxia. Change from adult to puppy behavior pattern	Unknown

COMMENT: WEINBERG and HALEY, Str. No. 94, and HALEY and McCORMICK, LSD No. 173, have previously reported on the effect of drugs given intracerebrally to dogs. The effects of i.c. injection in mice have also been reported by HALEY, LSD No. 250/Gy. The effects of i.c. injection in cats have been studied by BRADLEY and HANCE, LSD No. 227/BOL No. 16 and HANCE and BRADLEY, LSD No. 227a / BOL No. 16a.

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(Pharmakologische Wirkung intracerebral injizierter Pharmaka beim nicht-narkotisierten Tier)

Bei nicht-narkotisierten Hunden bewirkte intracerebrale (intraventriculäre) Injektion von Herzglykosiden (Str und Tryptaminstrophanthidin), Chinidin, Procainamid, Chlorpromazin, Reserpin und LSD starke Reizung des VNS. Gewisse Wirkungen waren allen Pharmaka gemeinsam, aber jedes löste auch spezifische Effekte aus, die offenbar in umschriebenen Hirnregionen lokalisiert waren. So verursachten die Herzglykoside sowohl EKG-Anomalien, die schliesslich in Kammerflimmern übergingen, als auch allgemeine Erregung (Wirkung auf den vorderen und hinteren Anteil des Thalamus?). LSD verursachte Ataxie und veränderte das Verhalten, sodass erwachsene Hunde sich wie junge benahmen (Angriffspunkt unbekannt). [Cf. WEINBERG & HALEY, Str. Nr. 94, Rapport 42/11 und HALEY & McCORMICK, LSD Nr. 173, Rapport 66 II/8. Ueber die Wirkung von intracerebralen Injektionen bei Mäusen berichtete HALEY, LSD Nr. 250/Gy, Rapport 76 II/7. Betreffs Wirkung intracerebraler Injektionen bei Katzen cf. BRADLEY & HANCE, LSD Nr. 227/BOL Nr. 16, Rapport 76 II/5 und HANCE & BRADLEY, LSD Nr. 227a/BOL Nr. 16a, Rapport Nr. 77 II/3.]

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