TABLE I. Effect of morphine on serum LH, FSH and prolactin levels in proestrous rats

Treatment	No. of rats	LH	FSH (mean ± S.E.) (ng/ml)	Prolactin
Saline	10	623 ± 105	206 ± 37	947 ± 154
Morphine	7	15 ± 3*	110 ± 11	144 ± 52*

*P < 0.001

decreased LH and FSH secretion and inhibits ovulation (6), it may be that morphine inhibits ovulation by decreasing the proestrous LH and FSH surges through effects on a central dopaminergic pathway. As the increased prolactin levels in plasma may cause a stimulation of hypothalamic prolactin inhibiting factor (PIF) synthesis and/or release, which is followed by an inhibition of prolactin release (7), and acute administration of morphine to male rats increases serum prolactin levels (8), morphine may suppress the proestrous serum prolactin surge by stimulating the PIF synthesis and/or release. The possibility of a direct action of morphine on the pituitary cannot be excluded and the mechanism of morphine which inhibits the proestrous LH, FSH and prolactin surges remains to be elucidated.

Our finding suggests the possibility that morphine blocks ovulation by inhibiting the preovulatory LH surge. The role of lowered FSH and prolactin levels of morphine-treated proestrous rats in the blockade of ovulation is now being investigated.

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INHIBITION OF PROSTAGLANDIN SYNTHETASE SYSTEM IN THE RABBIT RENAL MEDULLA BY PSYCHOTROPIC DRUGS

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It has been reported that chlorpromazine and desipramine, a major tranquilizer and antidepressant, respectively, exert anti-inflammatory activity in animals (1, 2) and that chlormezanone, a minor tranquilizer, has a more potent analgesic activity than aspirin (3). Vane has proposed that the pharmacodynamic activities of non-steroidal anti-in-

flammatory drugs are attributable to inhibition of prostaglandin (PG) biosynthesis (4) and many workers have confirmed that non-steroidal anti-inflammatory drugs possess the ability to inhibit PG biosynthesis (5-7). Recently, certain psychotropic drugs have been shown to inhibit PG biosynthesis *in vitro* (8, 9). In the light of these results, it is of interest to consider whether the inhibition of PG biosynthesis by psychotropic drugs is related to the anti-inflammatory and analgesic activities of these agents. We investigated the inhibition of PG synthetase system in the rabbit renal medulla (rabbit PSS) using chlormezanone, hydroxyzine, diazepam, chlorpromazine and desipramine, as representatives of minor or major tranquilizers and antidepressants.

Enzymatic activity was assayed in the following incubation mixture at 37 °C for 30 min: 7.5 mg of lyophilized microsomes of the rabbit renal medulla (rabbit PSS), 30 μ M 3 H-arachidonic acid, 1 μ M 14 C-dihomo- γ -linolenic acid, 1.7 mM reduced L-glutathione, 0.5 mM L-epinephrine, 0.07 mM EDTA-2Na and various concentrations of psychotropic drugs or reference compounds (aspirin and indomethacin) in 1.5 ml of 0.2 M Tris-HCl buffer (pH 7.5). PGs formed were extracted and separated by TLC, and the radioactivity of each spot on the TLC plate was measured by a liquid scintillation counter (10). Percent inhibition was obtained by comparing the percentage of radioactivity converted from the labeled substrates into PGs in the presence and absence of psychotropic drugs or reference compounds. IC₅₀ values were calculated from the equation of the best fit straight lines for log concentration vs. percentage inhibition plots, and represent the molar concentration of the drugs resulting in a 50% inhibition of PG biosynthesis.

As shown in Table 1, diazepam was the most potent inhibitor of psychotropic drugs tested, followed in decreasing order by chlorpromazine, hydroxyzine and desipramine. The inhibitory potencies of these drugs against PGE biosynthesis were similar to those against PGF biosynthesis. However, chlormezanone indicated no inhibition against the rabbit PSS in the concentration range from 0.1 to 3 mM. Diazepam and chlorpromazine were 11.1 and 4.9 times more potent than aspirin, respectively, with respect to their inhibition of

TABLE 1. Inhibitory effect of psychotropic drugs on PG biosynthesis *in vitro* by PG synthetase system in the rabbit renal medulla

Drugs	Inhibition of PG formation IC ₅₀ (μ M) ^a			
	PGE ₂	PGF _{2α}	PGE ₁	PGF _{1α}
Diazepam	89 ^b	117	243	113
Hydroxyzine	702	679	1000	735
Chlormezanone	inactive ^c	inactive	inactive	inactive
Chlorpromazine	203	184	240	188
Desipramine	1260	700	NT ^d	NT
Aspirin	984	977	721	687
Indomethacin	0.62	0.44	0.46	0.33

a) Molar concentrations inducing a 50% inhibition of PG biosynthesis.

b) Values represent the means for three experiments. c) Inhibition was nil in the concentration range from 0.1 to 3 mM. d) Not tested.

PGE₂ biosynthesis. The inhibitory potencies of hydroxyzine and desipramine were of the same order as aspirin. These four psychotropic drugs were much less potent than indomethacin, a potent anti-inflammatory drug. No clear-cut relationship was found among inhibitory potencies of minor and major tranquilizers and the antidepressant against the rabbit PSS. Since chlormezanone showed no inhibition of PG biosynthesis, its analgesic activity reported previously (3) may be induced by a secondary response to suppression of the central nervous system rather than by its PG synthetase inhibition. In the present study, diazepam was the most potent inhibitor of psychotropic drugs despite the lack of anti-inflammatory and analgesic activities (11). In addition, hydroxyzine which has appreciable analgesic activity but not anti-inflammatory activity (12), possessed only a weak ability to inhibit PG biosynthesis. From these results, it is conceivable that the anti-inflammatory activity shown by chlorpromazine and desipramine (1, 2) may be mainly induced by suppression of the central nervous system even if PG synthetase inhibition by both drugs may to some extent participate in the anti-inflammatory activity.

The inhibition of PG biosynthesis by the psychotropic drugs tested herein is apparently weak with little relation to the anti-inflammatory and analgesic activities.

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NEUROMUSCULAR BLOCKING ACTIONS OF NEUROTOXINS ISOLATED FROM LATICAUDA SEMIFASCIATA, NAJA NAJA AND NAJA NAJA ATRA —A COMPARATIVE ASSAY—

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Extensive pharmacological and toxicological studies on snake venoms have revealed that the venoms of most snakes belonging to the family of *Elapidae* and *Hydrophiidae* produce