While this study does not differentiate between skeletal muscle or the sympathetic nervous system as the primary site for drug induced malignant hyperthermia, it does suggest that the sympathetic nervous system (α-adrenergic receptor) is abnormal in stress susceptible swine. An enhanced sympathetic response could well explain the hypertension and enhanced heat production seen in the stress susceptible animal[6]. Since drugs which antagonize the sympathetic nervous system are effective in preventing the malignant hyperthermia, this suggests that the sympathetic nervous system may well play a key role in the syndrome.

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Analgesic dipeptide, L-Tyr-D-Arg (D-kyotorphin) induces Met-enkephalin release from guinea-pig striatal slices

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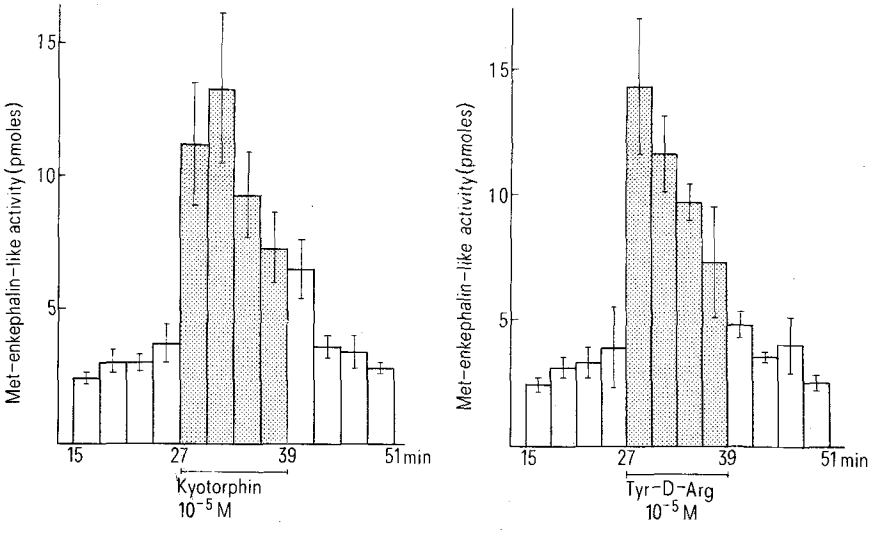
Summary. Kyotorphin (L-Tyr-L-Arg), an analgesic dipeptide isolated from the bovine brain, and its analogue, L-Tyr-D-Arg (D-kyotorphin) have a naloxone-reversible analgesic effect. Both peptides (10^{-5} M) induced an approximately 4-fold increase of the basal release of Met-enkephalin from striatal slices. Therefore they may produce their analgesic effects through release of Met-enkephalin. The stronger in vivo effect of D-kyotorphin may be explained by its resistance to degradation.

Kyotorphin (L-Tyr-L-Arg) is an analgesic dipeptide originally isolated from the bovine brain[2,3] using an in vivo analgesic assay method[4].

Kyotorphin reveals actions of the opioid type including analgesic effects[5,6]; these opioid actions can possibly be explained on the basis of an enkephalin release but not on the basis of interaction with opiate receptors[3,7]. The analogue L-Tyr-D-Arg (D-kyotorphin), which is stable enzymatically in the brain, also produces a naloxone-reversible analgesia when administered intracisternally to mice[8].

Recently, Laubie and Schmitts[9] reported that D-kyotorphin, given into the nucleus ambiguus in the dog produced a vagal bradycardia which was reversed by naloxone. In an attempt to examine the possible mechanism of these opioid actions, we investigated the effect of D-kyotorphin on the enkephalin release. Experiments to determine the release of enkephalin were performed using the guinea-pig striatal slices. The release experiments were carried out as described recently[7]; the radioimmunoassay used for the determination of Met-enkephalin had a sensitivity of 1 fmole/tube and the overall recovery of the procedure was $87 \pm 6\%$ ($n = 6$).

Kyotorphin and D-kyotorphin induced Met-enkephalin release at rates of approximately 4 times basal release (fig.)



Effects on the Met-enkephalin release from the guinea-pig striatal slices.

when both enkephalin degrading enzymes, enkephalinase and aminopeptidase were completely inhibited in the presence of the mixture of dipeptides[7,10]. Lindberg and Dahl[11] did not detect a kyotorphin-induced Met-enkephalin release when using bacitracin as a peptidase inhibitor. However, bacitracin (about 4.3×10^{-5} M) might be a less potent peptidase inhibitor than the mixture of dipeptides (each 1 mM)[10], therefore the added kyotorphin and released Met-enkephalin may have been degraded during the superfusion.

It has been reported by several investigators that endogenous opioid peptides are involved in the response to the nociceptive stimuli[12,13]. Most recently Kuraishi et al.[14] demonstrated that during the nociceptive stimuli, Met-enkephalin is released from the nucleus reticularis gigantocellularis of the rat medulla oblongata, a most sensitive site to the analgesic effects of morphine and enkephalin[15,16], thereby suggesting that enkephalin may play a role in pain regulation. Our present data suggest that both kyptorphin and D-kyotorphin produce analgesic effects by the induction of Met-enkephalin release. However, D-kyotorphin shows higher in vivo analgesic activity than does kyotorphin[8,9], despite the finding that both dipeptides are equipotent regarding enkephalin release. In preliminary experiments it was shown that kyotorphin (10^{-5}-10^{-3}M) was completely degraded within 10 min when incubated with S_2-fraction or P_2-fraction of the rat brain at 37 °C. In contrast, D-kyotorphin (10^{-5}M) remained intact after incubation for 60 min in these brain fractions. The more powerful action of D-kyotorphin can therefore be explained by the fact that it is more stable in the brain fractions than kyotorphin.

Thus, D-kyotorphin can probably serve as a useful tool for investigating the involvement of enkephalin in a variety of behavioral situations and may even represent the prototype of a new class of pharmacological agents.

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Bioavailability of norethindrone in women and rabbits after administration of norethindrone acetate through the subcutaneous route

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Summary. The levels of available norethindrone were found to be similar in women and rabbits after s.c. administration of crystalline and amorphous norethindrone acetate respectively, and this study indicates that the rabbit may be used as an animal model for further investigation with this contraceptive steroid.

Norethindrone (NET), a biologically active metabolite of norethindrone acetate (NETA) is reported to be available in the plasma of animals[2] and women[3,4] after s.c. insertion of a silastic implant containing NETA. The present study is a comparison between the availability of NET in the serum of women and rabbits after administration of allomorphs of NETA through the s.c. route, to examine whether the rabbit could be used as an animal model for pharmacological and toxicological studies of this contraceptive steroid.

Materials and methods. Polydimethyl siloxane (silastic) implants-D were prepared with 40 mg crystalline or amorphous NETA according to the method described elsewhere[5]. Groups of 6 women and 6 New Zealand breed female albino rabbits were selected for this study. A single silastic implant containing crystalline NETA was s.c. inserted in the thigh of each woman under local anesthesia with 2% xylocaine. Similarly, an implant containing amorphous NETA was inserted in the thigh of a hind leg of each rab-

Serum NET levels (ng/ml) after insertion of an implant containing 40 mg NETA

		Treatment period (in weeks) 1	2	3	4	6	8	10	12	14	16	18	
Women mean	(n=6)	-	1.2	-	1.7	1.4	1.5	1.2	1.2	1.0	0.9	-	
Women mean ± SD		-	0.5	-	0.6	0.4	0.8	0.5	0.4	0.2	0.6	-	
Rabbits mean	(n=6)	3.1	3.8	1.4	1.4	1.1	0.9	1.0	1.1	0.8	1.0	0.7	$p > 0.1$*
Rabbits mean ± SD		0.8	2.3	0.3	0.6	0.4	0.2	0.5	0.1	0.1	0.2	0.4	

n, Number of samples, *not significant.