Table 1. *Pharmacokinetics of* R *and* S*-phenprocoumon in man after single oral dosing (50 mg).*

Subject	Weight (kg)	Enantiomer	Half-life* (h)	Zero-time plasma concn* (mg litre^{-1})	Apparent volume of distribution* (% body wt)	Clearance† (ml min^{-1} kg^{-1})
I	71	*R*	93	8·9	7·9	0·0098
		S	145	8·9	7·9	0·0062
II	77·7	*R*	101	6·3	10·2	0·0116
		S	104	9·1	7·1	0·0079
III	74	*R*	82	8·3	8·1	0·0116
		S	117	6·2	10·9	0·0110
IV	71	*R*	133	7·2	9·8	0·0085
		S	241	8·5	8·3	0·0039
V	73	*R*	145	5·3	12·9	0·0103
		S	115	7·0	9·8	0·0098
Mean with s.d.		*R*	110·8 s.d. 26·9	7·2 s.d. 1·46	9·78 s.d. 2·02	0·0103 s.d. 0·0013‡
		S	144·4 s.d. 56·1	7·94 s.d. 1·27	8·8 s.d. 1·53	0·0076 s.d. 0·0028

Plasma phenprocoumon was determined according Lewis & others (1970).
* Determined as described by Hewick & McEwen (1973).
† Calculated by dividing apparent volume of distribution (ml kg^{-1}) by half-life (min) and multiplying by 0·693.
‡ Significantly different (paired *t*-test) from corresponding value for *S*-phenprocoumon.

McEwen, 1973; Breckenridge, Orme & others, 1974; O'Reilly, 1974).

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Accumulation of cGMP in striatum of rats injected with narcotic analgesics: antagonism by naltrexone

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The stereospecific binding of some narcotic analgesics to a protein present in different amounts in homogenates of various brain structures has many physicochemical features expected of a drug binding to a specific site. Since the affinity constant for this binding in many drugs relates to their analgesic activity, the concentration of such receptors in brain structures reflects a site for the specific action of narcotic analgesics (Pert & Snyder, 1973). Although the necessary criteria that define ligand recognition have been satisfied (Creese, Pasternak & others, 1975), the molecular mechanisms that are regulated by the binding of opiates to this receptor are still undefined. It is possible that opiate receptors can be identified with specific postsynaptic receptors for a transmitter which carries information concerning pain. When the distribution of the opiate receptor in various nuclei of the cns is compared with that of known neurotransmitters a certain similarity can be found between the distribution of GABA (γ-aminobutyric acid) or acetylcholine and that of the opiate receptor (Snyder & Pert, 1975).

That a specific transmitter, involved in the mediation of pain sensation may be the natural agonist for opiate receptors is suggested by the following considerations:

(1) naloxone and other opiate antagonists displace the opiate from the specific brain receptor with an affinity related to their potency as analgesic antagonists (Pert & Snyder, 1973); (2) a polypeptide with molecular weight of about 1000 has been isolated from brain; this peptide mimics the action of morphine on guinea-pig ileum (Hughes, Smith & others, 1975) and, (3), this action is antagonized by naloxone (Hughes & others, 1975); (4) a polypeptide which mimics morphine on the ileum preparation was isolated from pituitary and displayed a high affinity binding for the opiate receptor (Teschemacher, Opheim & others, 1975); (5) the brain contains a substance that like morphine binds to the opiate receptor, the concentrations of this substance are high in striatum and low in cerebellum (Pasternak, Goodman & Snyder, 1975).

Morphine increases the content of 3′,5′-guanosine monophosphate (cGMP) and decreases that of 3′,5′-cyclic adenosine monophosphate (cAMP) in neuroblastoma cell lines (Gullis, Traber & Hamprecht, 1975). Since in brain the opiate receptor may exist in two conformational states (sodium dependent and sodium free) (Pasternak & Snyder, 1975) it was suggested that each of the two conformational states of the opiate receptor was linked in its function with either cAMP or cGMP.

Morphine in very high doses increases the cAMP content of striatum (Costa, Carenzi & others, 1973). Since the doses of morphine required were high, perhaps they were unrelated to a specific binding of morphine to the opiate receptor. Other reports (Bonnet, 1975) have shown that morphine increases cAMP content and decreases cGMP content in various brain structures including striatum. However, since in the methods used inactivation of brain enzymes did not occur in less than 10 s, the results cannot be readily extrapolated to the *in vivo* situation. We now report on the actions of various doses of analgesics on the cGMP content of striatum in rats killed with microwave radiation to inactivate brain enzymes in less than 2 s (Guidotti, Cheney & others, 1974).

Sprague Dawley male rats, 150 g, kept on circadian light at 23° were injected with various drugs and killed at various times thereafter. The cGMP content of striatum and other brain structures was measured (Mao, Guidotti & Costa, 1974a). The stimulation of postsynaptic receptors by transmitter agonists can increase the concentration of cAMP or cGMP in postsynaptic cells (Siggins, Battenberg & others, 1973; Guidotti, Hanbauer & Costa, 1975). In homogenates of pineal (Weiss & Costa, 1967) and striatum (Kebabian, Petzold & Greengard, 1972) the addition of neurotransmitters mediating synaptic activity in these structures activates adenylyl cyclase.

The data in Table 1 show that morphine, when given in analgesic doses (35–105 μmol kg^{-1}, s.c.) enhanced the cGMP content of striatum. These doses fail to change the cAMP content of striatum (Costa & others, 1973). Haloperidol (4 μmol kg^{-1}, i.p., 20 min before morphine), trihexyphenidyl (29 μmol kg^{-1}, i.p., 30 min before); reserpine (8 μmol kg^{-1}, i.v., 2·5 h before) neither changed the cGMP content of striatum nor blocked the increase of cGMP produced by morphine. Naltrexone, a morphine antagonist fails to increase the cGMP content of striatum but completely blocks the cGMP increase elicited by morphine (Table 1). The increase of striatal cGMP elicited by morphine lasts longer than 40 min.

The action of morphine is shared by azidomorphine and viminol (R_2) but not by the non analgesic stereoisomer viminol (S_2) the cGMP content (pmol mg^{-1} protein) in rats being: saline (5 ml kg^{-1}, i.p.) 0·72 ± 0·06; morphine (70 μmol kg^{-1}, s.c.) 2·1 ± 0·27 ($P<0·01$); azidomorphine (0·64 μmol kg^{-1}, s.c.) 2·0 ± 0·16 ($P<0·01$); viminol R_2 (17 μmol kg^{-1}, i.p.) 1·3 ± 0·07 ($P<0·01$), viminol S_2 0·69 ± 0·04; means of 5–8 experiments, animals injected 20 min before death. It appears that this action on striatal cGMP content relates to the potency of the analgesic activity (Knoll & Zsilla, 1974; Della Bella, Ferrari & others, 1973).

Morphine (Costa & others, 1973), like haloperidol (Zivkovic, Guidotti & others, 1975) accelerates the turnover rate of striatal dopamine. However, the action of morphine can be differentiated from that of haloperidol because *in vitro*, haloperidol blocks the activation of adenylate cyclase by dopamine, morphine does not (Carenzi, Guidotti & others, 1975b). In addition, haloperidol antagonizes the increase in striatal cAMP content elicited by apomorphine and (+)-amphetamine

Table 1. *Striatal cGMP content in rats at different times after morphine injection (dose response) and in rats receiving morphine or morphine + naltrexone (3 μmol kg^{-1}, i.p.) 25 min after morphine (time course).*

Time course		Dose response§		
Time (min) after morphine (70 μmol kg^{-1}, s.c.)	cGMP† (pmol mg^{-1} protein)	Morphine μmol kg^{-1}, s.c.	cGMP‡ (pmol mg^{-1} protein)	
			Saline	Naltrexone
0	0·52 ± 0·02	0	0·58 ± 0·06	0·84 ± 0·09
5	1·11 ± 0·10*	17·5	0·76 ± 0·09	—
10	1·2 ± 0·11*	35	1·1 ± 0·11*	—
20	1·1 ± 0·13*	70	1·5 ± 0·12*	0·77 ± 0·10
40	1·4 ± 0·12*	105	1·6 ± 0·10*	—

Each value is the mean ± s.e. of 5† or 8‡ expt. * $P<0·01$. § The animals were killed 40 min after morphine.

whereas morphine does not (Carenzi, Cheney & others, 1975a). Finally, haloperidol increases the turnover rate of striatal acetylcholine (Racagni, Cheney & others, 1976) whereas morphine does not (Cheney, Trabucchi & others, 1974).

GABA is an inhibitory putative neurotransmitter that is present in striatum (Fonnum, Grofova & others, 1974). Blockade of GABA synthesis by isoniazid increases the cGMP content of striatum (Biggio & Guidotti, 1976) and cerebellum (Mao, Guidotti & Costa, 1974b). Thus, one might infer that morphine action might cause directly or indirectly an inhibition of GABA transmission. The specificity of the morphine effects on cGMP and GABA system of striatum could be argued. Isoniazid which blocks GABA synthesis in every brain part, for instance, increases the cGMP content in cerebellar cortex, deep cerebellar nuclei and striatum (Biggio & Guidotti, 1976). In contrast, morphine increases cGMP content in striatum and nucleus accumbens but not in cerebellar cortex and deep cerebellar nuclei (unpublished observations). This evidence suggests that if morphine inhibits the GABA system in striatum its action is probably indirect. It is important to note that cerebellum is practically devoid of opiate receptors whereas striatum is one of the areas that have an abundant opiate receptor content (Pert & Snyder, 1973). Since morphine fails to change the cGMP content in cerebellum, a direct action of the drug on guanyl cyclase can not be the mechanism whereby these analgesics affect the cGMP content of striatum. Whether the increase in striatal cGMP content is related to an activation of opiate receptors or is mediated by an inhibition of GABA system elicited through the activation of opiate receptors remains to be established.

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