in HOAc (5 ml) was desalted with H_2S for 2 min. The filtrate was dried up to a crude powder melting above 183°. Yield: 43 mg. Positive to ninhydrin test. *Rf* 0.71 on paper. Purification of the compound (IVa) was carried out by cellulose column (2.6×55 cm) using *n*-BuOH-saturated water (*Rf* 0.56 on paper). Yellow precipitate corresponding to IVa was obtained during the concentration. IR ν_{max}^{KBr} (cm^{-1}): 3400, 2980, 1705, 1615, 1590, 1490, 1420, 1330, 1180, 1125, 1050, 920, 830, 740 in its hydrochloride. NMR (D_2O) δ: 1.9 m. 4H, 2.90 d. J=6 Hz 2H, 3.65 t. J=6 Hz 2H, 3.76 m. 1H, 7.18 d. J=11 Hz 1H, 8.35 d. J=11 Hz 1H, 9.12 s. 1H in hydrochloride.

Synthesis of IVb——The complex (II) was benzoylated in 5% $NaHCO_3$ with cooling to precipitate a greenish powder corresponding to IIIb (*Rf* 0.59 on paper). The precipitate was filtered and washed with water and ether. The intermediate IIIb was dissolved in HOAc, and desalted with H_2S. The filtrate was evaporated to a crude powder, TLC on silica gel: *Rf* 0.30 (MeOH). Further purification was achieved with cellulose column (2.5×60 cm). Fractions showing one spot (by ninhydrin test) were collected and evaporated to a small volume, and precipitated with EtOH, ether, and pet. ether. IR ν_{max}^{KBr} (cm^{-1}): 2940, 1715, 1630, 1570, 1540, 1490, 1410, 1310, 1215, 1180, 1160, 715 in hydrochloride. NMR (D_2O) δ: 1.75 m. 4H, 2.79 d. J=6 Hz 2H, 3.40 t. J=6 Hz 2H, 3.65 m. 1H, 7.5—7.86 m. 5H in hydrochloride. NMR of L-β-lysine hydrochloride as reference δ: 1.70 m. 4H, 2.72 d. J=6 Hz 2H, 2.98 t. J=5.5 Hz, 3.57 m. 1H.

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Mode of Action of Analgesic Effect of 2-Methylaminomethyl-2,3-dihydrobenzofuran (EPS-4032)

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Through our intensive pharmacological screening of benzofuran derivatives, we found that 2-monoalkylaminomethyl-2,3-dihydrobenzofuran analogues, especialy, 2-methylaminomethyl-2,3-dihydrobenzofuran (EPS-4032) revealed relatively potent analgesic effect.[2]

The purpose of our present work was to investigate the mode of action of analgesic effect of EPS-4032 in mice comparing with morphine.

Method

The analgesic effect of these drugs were tested by means of the electrical stimulation method (40 volt, 20 msec, 1 Hz) in male mice weighing 14—16 g.[3]

Result and Discussion

As shown in Table I and Fig. 1, analgesic effect of EPS-4032 as well as morphine was apparently antagonized by pretreatment of reserpine or tetrabenazine. Several studies suggest that the analgesic effect of morphine result from an interaction with brain mono-

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Table I. Analgesic Effects of EPS-4032 and Morphine combined with Various Drugs in Mice

Combined drugs	Analgesic effect (AD-50) in mice	
	EPS-4032 (mg/kg)	Morphine (mg/kg)
—	31.0 (27.7—34.7)	2.3 (2.0—2.7)
Tetrabenazine 40 mg/kg (*i.p.*)	50 [2/23]	5.0 [0/10]
Reserpine 2.0 mg/kg (*s.c.*)	50 [2/12]	5.0 [0/10]
Levallorphan 10 mg/kg (*i.p.*)	10.8 (8.3—14.0)	5.0 [1/10]
Nialamide 20 mg/kg (*i.p.*)	11.7 (9.9—13.8)	4.0 [1/11]

[ ]: Number of animals showed analgesia/Number of used animals.

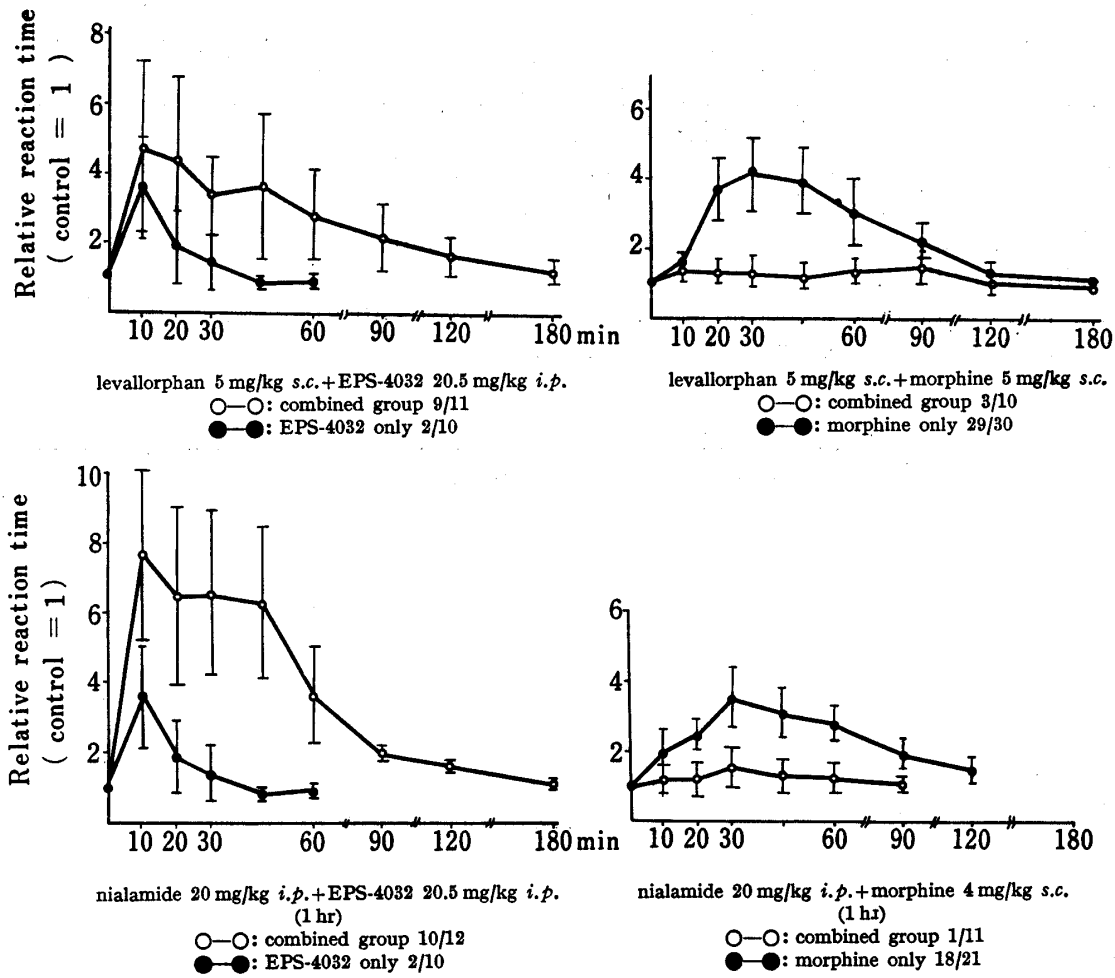

Fig. 1. Analgesic Activities of EPS-4032 and Morphine combined with Levallorphan or Nialamide tested by Electrical Stimulation Method in Mice

amines.[4-6] Therefor, these results suggest that the brain monoamines act an important role in the analgesic action of EPS-4032 like morphine.

In our present experiment, it was found that the analgesic effect of morphine was clearly antagonized with not only levallorphan, one of opioid antagonist, but also nialamide, a monoamine oxidase inhibitor (MAO-I). On the other hand, the analgesic effect of EPS-4032 was antagonized neither levallorphan nor nialamide, but markedly potentiated by them.

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It has been reported that the toxicity of morphine increase in the animals pretreated with MAO-I.[7] But our experiment showed that morphine analgesia was significantly decreased in mice pretreated with nialamide. Recently, Vedernikov and Afrikanov have reported that iproniazid weakened the analgesic action of morphine in rats.[8] The mechanism of the antagonism between morphine and nialamide has not yet been clear. However, it seems resonable that MAO-I antagonized morphine analgesia, since the inhibition of MAO could inhibit the release of noradrenaline or reduse the turnover of it.[9]

Levallorphan are known to antagonize the analgesic action of morphine. In previous papers,[3,10] we have reported that the analgesic effects of some antipyretic analgesics, such as aminopyrine, were markedly potentiated by levallorphan in mice. Also Inukai and Takagi[11] have reported that the analgesic effect of aminopyrine was significantly potentiated by nalorphine and suggested that since the microsomal drug-metabolizing enzyme sytem are inhibited by nalorphine,[12] the inhibition of inactivation of aminopyrine by it may be one of possible mechanism. Although it has not known that whether levallorphan inhibit drugmetabolizing enzymes, the similar mechanism may be considered in the case between levallorphan and aminopyrine or EPS-4032.

Since nialamide inhibit not only MAO activity in brain and liver but also the activities of microsomal drug-metabolizing enzyme system in liver,[13] it has been considered that potentiation of the analgesic effect of EPS-4032 by nialamide is relating to the inactivation of it in brain and or liver.

The facts[14] that the analgesic effect of EPS-4032 was apparently increased by pretreatment of SKF-525A and decreased by pretreatment of phenobarbital, also support above consideration.

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