circulation des substances morphogènes entre les blastomères. Cette circulation fondant l'unité organique de la larve en harmonisant les activités des différents blastomères, toute perturbation à ce niveau peut entraîner des modifications dans la proportion relative des structures ectodermiques et entomésodermiques.

Nous rappellerons, pour terminer, que l'acide thiomalique modifie également la différenciation de l'œuf d'amphibien; il suscite en effet la formation de structures chordomésoblastiques à partir d'ectoblaste présomptif[13,14]. Il serait intéressant de rechercher si Thiola est également capable de provoquer de telles modifications chez l'amphibien. Les résultats déjà obtenus avec l'acide thiomalique suggèrent l'existence d'une base commune aux processus régulateurs de la différenciation chez les amphibiens et les échinodermes.

Summary. 2-Mercaptopropionyl-glycine (Thiola) exerted a strong animalizing action on the development of the sea urchin, *Paracentrotus lividus*. The action of Thiola on the synthesis of superficial and cortical cellular structures newly synthesized during the segmentation is suggested. These changes may alter the circulation of morphogenetic substances between blastomeres.

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Influence of Adrenergic Blocking Agents Upon Morphine and Catecholamine Analgesic Effect

The mechanism of the analgesic action of morphine is still unknown. Several theories have been proposed, but they are not satisfactory as yet.

Some authors[1–3] postulate that the analgesic effect of morphine is mediated by parasympathic mechanisms. MERCIER et al.[4] and others[5] believe that serotonin is an important neurohumoral agent concerning these effects. Since MARTHA VOGT reported in 1954[6] that morphine reduces the amount of catecholamines in the brain, many authors have supposed that these agents exert an enhancing influence on the analgesic effect of morphine. Also, some authors reported that epinephrine and related substances possess a significant analgesic efficacy of their own[7–10]. On the other hand, the monoamine oxidase inhibitor iproniazid enhances[11] and reserpine diminishes[12–14] the analgesic effect of morphine. It is well known that these drugs raise and lower, respectively, the catecholamine content of the brain. Unfortunately, we know almost nothing about the nature of the adrenergic receptors involved in the central actions of catecholamines[15].

We therefore proposed to study: (1) the proper analgesic effect of catecholamines; (2) their effect upon the analgesic action of morphine, and (3) the influence of adrenergic blocking agents of α and β type upon the catecholamine and morphine analgesic effects, using the α-blocking agent dihydroergotamine and the β-blocking agent propranolol, both drugs having powerful actions upon the central nervous system of mammals[16,17].

Method. We used a method based on that of JANSSEN[18], BEN-BASSAT et al.[19] and GREEN et al.[20]. We employed white female mice, weighing 17–30 g. The painful stimulus consisted of warm water (50 $\pm$ 1 °C) applied to the tail of the animals. Untreated animals removed their tail from the warm water with a sharp movement (tail withdrawal reflex) within the first 3–4 sec of exposure. The same animals were then treated with drugs and the reaction time was measured again every 15 min until the effect disappeared. The drugs were dissolved in distilled water and administered i.p. The time of reaction to the painful stimulus was measured in sec and the standard deviation of the mean was determined. Each group consisted of 6 animals. The injection of distilled water alone did not modify the reaction time.

Results. (1) Effect of morphine and catecholamines. Morphine showed a significant analgesic effect at a dose of 1 mg/kg, i.p. Also the catecholamines epinephrine, norepinephrine and isoproterenol produced significant analgesic effects in this test. The minimal doses with significant analgesic effect were: epinephrine 0.25 mg/kg, norepinephrine 0.5 mg/kg and isoproterenol 4 mg/kg.

Catecholamines enhanced the effect of small doses of morphine (1 mg/kg), epinephrine and norepinephrine increasing the duration and the maximum of morphine analgesic effect, but isoproterenol only increased the duration of the significant effect from 45–105 min without affecting its maximum. We have not demonstrated a potentiation for higher doses of morphine (2.5 mg/kg).

(2) Effect of α- and β-adrenergic blocking agents. Propranolol and dihydroergotamine were used at doses that

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Influence of catecholamines and α- and β-adrenergic blocking drugs upon the analgesic action of morphine in mice

Drug mg/kg	Control	Maximum effect	Increase of reaction time (sec)	(%)	Duration of the effect, significant for $P < 0.02 > 0.001$ (min)
Distilled water	2.6 ± 0.4	3.0 ± 0.5	0.4	15	–
Morphine 1.0	3.3 ± 0.2	5.3 ± 0.4	2.0	60	45
Morphine 2.5	3.8 ± 0.3	9.0 ± 0.6	5.2	136	150
Epinephrine 0.25	2.8 ± 0.5	5.0 ± 0.2	2.2	78	15
Epinephrine 0.50	3.1 ± 0.4	7.0 ± 0.6	3.9	125	120
Norepinephrine 0.50	2.6 ± 0.2	4.4 ± 0.3	1.8	69	15
Norepinephrine 1.0	2.1 ± 0.3	4.3 ± 0.4	2.2	104	120
Isoproterenol 4.0	3.0 ± 0.3	4.6 ± 0.1	1.6	53	15
Isoproterenol 8.0	3.1 ± 0.4	5.7 ± 0.7	2.6	83	60
Morphine 1.0 + epinephrine 0.25	4.7 ± 0.6	11.1 ± 0.9	6.4	136	135
Morphine 1.0 + norepinephrine 0.5	3.2 ± 0.4	6.4 ± 0.4	3.2	100	105
Morphine 1.0 + isoproterenol 4.0	3.0 ± 0.2	5.2 ± 0.5	2.2	73	105
Dihydroergotamine 4.0	4.0 ± 0.4	4.7 ± 1.0	0.7	17	–
Propranolol 1.0	3.3 ± 0.2	3.8 ± 0.8	0.5	15	–
After dihydroergotamine 4 mg/kg					
Morphine 2.5	3.3 ± 0.2	9.2 ± 1	5.9	178	150
Epinephrine 0.50	3.6 ± 0.3	5.7 ± 0.2	2.1	58	120
Norepinephrine 1.0	3.4 ± 0.2	6.0 ± 0.4	2.6	79	90
Isoproterenol 8.0	4.9 ± 0.4	7.5 ± 0.3	2.6	53	120
After propranolol 1 mg/kg					
Morphine 2.5	4.1 ± 0.2	6.6 ± 0.4	2.5	60	30
Epinephrine 0.50	3.6 ± 0.6	4.5 ± 0.5	0.9	25	–
Norepinephrine 1.0	3.4 ± 0.4	5.2 ± 0.5	1.8	52	–
Isoproterenol 8.0	3.4 ± 0.5	4.0 ± 0.6	0.6	17	–

The blocking agents were administered together with the agonists. Results represent the time for the withdrawal reflex to occur after exposure to the warm water (50 °C). Each number is the mean of a group of 6 animals, ± the standard deviation of the mean. Significance is referred to control values. The increase of reaction time is expressed as sec and % of increase (referred to control values).

by themselves did not modify the reaction time (1 and 4 mg/kg, respectively). Dihydroergotamine did not reduce the analgesic effect of morphine, nor that of isoproterenol. It only slightly decreased the duration of the analgesic effect of norepinephrine (from 120–90 min). The analgesic effect of epinephrine was quantitatively diminished, but remained statistically significative and its duration was not affected. On the other hand, the β-adrenergic blocking agent propranolol (1 mg/kg) significantly decreased the analgesic effect of 2.5 mg/kg of morphine and completely blocked the effect of epinephrine and isoproterenol, while it did not diminish so much the effect of norepinephrine. However, the analgesic effect of norepinephrine, after a combination with propranolol, was no longer significant.

Discussion. Our results are in accordance with those of other authors[6–8,10,21], in the sense that catecholamines play an important role in the mechanism of the analgesic effect of morphine. We confirmed that catecholamines have an analgesic effect of their own[8]. A central site for these actions cannot be excluded, for ROTHBALLER[10] has shown that the passage of catecholamines across the hematoencephalic barrier is not so difficult as it was generally thought.

While the α-adrenergic blocking agent dihydroergotamine did not substantially change the analgesic effects of catecholamines and morphine, the β-adrenergic blocking agent propranolol blocked not only the analgesic effects of catecholamines, but also that of morphine itself. Therefore, we think that central adrenergic receptors similar to the β type of the periphery might be involved in these actions of catecholamines, and also in the mechanism of morphine analgesic effect.

Resumen. Las catecolaminas adrenalina (0,25 y 0,5 mg/kg) noradrenalina (0,5 y 1 mg/kg) e isoproterenol (4 y 8 mg/kg) producen efecto analgésico significativo en lauchas. También aumentan (adrenalina 0,25 mg/kg, noradrenalina 0,5 mg/kg e isoproterenol 4 mg/kg) el efecto analgésico de pequeñas dosis de morfina (1 mg/kg). El bloqueador α-adrenérgico dihidroergotamina (4 mg/kg) no influencia substancialmente estas acciones, pero el bloqueante β-adrenérgico propranolol (1 mg/kg) bloquea los efectos analgésicos de la morfina, adrenalina e isoproterenol, no siendo tan efectivo contra la noradrenalina. Se deduce que debe existir un compromiso de receptores β-adrenérgicos en el mecanismo de los efectos analgésicos de las catecolaminas y también de la morfina.

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