weighed, and dissolved in tissue solubilizer for assay of radioactivity. Data were expressed as counts per minute per milligram of tissue (wet weight). This figure varied severalfold between birds, probably because of the difficulty of ensuring the precise location of the injection needle within the heart. Results were calculated as the ratio of radioactivity in the right (R) brain region relative to that in the left (L) region. To avoid skewing data the natural logarithm of this ratio was determined for each bird (ln R/L). The antilogarithms of the final mean logarithmic ratio (that is, the geometric mean) constitute the data presented (Table 1). The rate of blood flow through the hemisphere contralateral to the eye exposed to the learning situation for the first time was significantly greater than that in the opposite hemisphere, whereas no such major asymmetry was detected between pairs of optic lobes.

A second series of experiments was conducted that was almost identical to that described above except that in the second 5 minutes a test bowl containing solely grains was substituted for the bowl containing the grain and stone mixture. In this case the bird's feeding did not involve any discrimination task. No significant asymmetry of blood flow was detected between pairs of brain regions under these control conditions (Table 1).

Blood flow data derived from the discrimination studies were compared to those obtained from the control series involving feeding without discrimination (Table 1). The asymmetry of blood flow between hemispheres of chicks in the discrimination situation was marginally statistically different from the corresponding values for control chicks ($P = .065$; t-test, one-tailed). This last figure for control conditions was close to unity. However, the probability that asymmetry of blood flow in experimental birds was significantly different from unity was much greater ($P < .01$, Table 1). The one-tailed t-test was used because previous experiments had suggested that there might be a positive correlation between new arousal and cerebral blood flow. The naive hemisphere would be expected to be freshly alerted by exposure to the task. The production of a difference in blood flow between the two brain hemispheres was therefore demonstrable only in the visual discrimination situation. It was possible to obtain metabolic differences in the two brain halves without concomitant asymmetry of sensory input or behavioral response. The variation in blood flow observed between pairs of hemispheres may be attributable to the different prior experiences of these regions. There is evidence that the engram for a monocularly learned behavior in the chick is confined to a single cerebral hemisphere (*9*). The excess blood flow we have observed in the "naive" hemisphere may reflect the activation of the hemisphere in which no engram is present. Such changes in the supply of nutrients to the brain could underlie the accretion of RNA and protein reported to be a consequence of environmental enrichment or behavioral challenge (*11*).

There are several suggestions of increased rates of macromolecule synthesis associated with learning phenomena (*11*), but many nonspecific factors can obscure comparison between individual animals in differing environmental situations. The changed rate of blood flow we have described cannot be attributed to variation in the intensity or quality of sensory input or to a changed humoral content of circulating hormones. Nor can the data be accounted for in terms of altered animal arousal or motor activity. Our results suggest that the presentation of a visual discrimination task can modify cerebral metabolism.

Table 1. Relative rates of blood flow in the right (R) and left (L) sides of the chick brain 10 seconds after intracardiac injection of [^{14}C]antipyrine. Blood flow rates were determined as counts per minute per milligram of tissue. The chicks had learned a discrimination task with the left eyelids sutured; 3 hours later they were reexposed to the discrimination task for 5 minutes while control birds were merely given grain. Both groups of birds had both eyes open while blood flow was determined. Results are the mean of 33 experimental or 29 control birds ± standard error.

Group	R/L	
	Cerebral hemispheres	Optic lobes
Experimental	1.15 ± .06*	1.07 ± .07†
Control	1.04 ± .04†	1.02 ± .05†

*$P < .01$ that value is significantly above unity (Student's one-tailed t-test). †Not significantly above 1.0.

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Guanosine 3′,5′-Monophosphate: A Central Nervous System Regulator of Analgesia

Abstract. *The dibutyryl derivative of guanosine 3′,5′-monophosphate (cyclic GMP), administered centrally, totally abolishes response to noxious stimuli without depressing the central nervous system. Analgesic properties of the nucleotide are not reversed by naloxone. Microinjected intracerebrally into different sites, dibutyryl cyclic GMP does not mimic the action of morphine. Pharmacological effects of dibutyryl cyclic GMP suggest that endogenous cyclic GMP modulates an inhibitory pain pathway distinct from that on which morphine acts.*

The search for the endogenous ligand of the opiate receptor has recently focused scientific interest on naturally occurring peptides (*1*) possessing the beneficial as well as the harmful properties of the opiates (*2*). We have discovered that the dibutyryl derivative of the naturally occurring cyclic nucleotide guanosine 3′,5′-monophosphate (dibutyryl cyclic GMP) administered directly into the central nervous system protects against noxious stimuli without inducing sedation, depressing respiration, or altering either awareness (as manifested by response to auditory and visual stimuli) or locomotor activity; and protects against nociperception and mortality resulting from high temperatures. Unlike those of the opiates, the analgesic properties of dibutyryl cyclic GMP are neither prevented nor reversed by naloxone.

Information on cyclic GMP has been

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Table 1. Comparison of the effects of morphine sulfate and dibutyryl cyclic GMP administered in a volume of 15 μl into a lateral ventricle. Groups of ten rats were injected with the indicated doses (in nanomoles of morphine and cyclic GMP). The mean time to onset of analgesia as tested by tail clamp was 0.18 ± 0.03 hour for morphine and 0.04 ± 0.01 hour for dibutyryl cyclic GMP. Although the nucleotide-induced onset was four to five times faster than that of morphine, on a molar basis, morphine was four to five times more potent than the nucleotide. We have no explanation for these differences in dose responses. The durations of analgesia of morphine (3.7 ± 1.15 hours) and dibutyryl cyclic GMP (3.6 ± 1.28 hours) were similar. Respiratory depression, muscular rigidity, and sedation occurred in all rats tested with 26 to 78 nmole of morphine; increasing doses increased the severity of the behavioral symptoms. Total movements for 240 minutes were recorded with a Stoelting electronic activity monitor. Each value represents the mean ± standard deviation obtained in a group of three rats. Freehand intracerebroventricular injections (*14*) and injections through stereotaxically implanted cannulas yielded similar results in similar dose ranges.

Treatment	Dose (nmole)	Loss of squeak-struggle response	Loss of eyelid and corneal reflexes	Respiratory depression	Muscular rigidity	Sedation	Total movements for 240 minutes
Morphine sulfate	13.5	None	None	10/10	None	10/10	14,500 ± 1,174
	26	2/10	10/10	10/10	10/10	10/10	6,794 ± 540*
	52	5/10*	10/10	10/10	10/10	10/10	1,355 ± 274*
	78	10/10	10/10	10/10	10/10	10/10	876 ± 204*
Dibutyryl cyclic GMP	88.6	None	None	None	None	None	14,600 ± 811
	118.2	1/10	None	None	None	None	12,894 ± 478
	147.8	5/10*	None	None	None	None	15,184 ± 781*
	177.3	8/10*	None	None	None	None	12,750 ± 692
	354.6	10/10	None	None	None	None	13,718 ± 356
Saline vehicle		None	None	None	None	None	13,295 ± 466

*$P < .05$; Dunn statistic for multiple comparisons.

accumulated slowly. It was first identified as a natural occurrent in rat urine in 1963 (*3*) and in mammalian tissue in 1969 (*4*), and additional findings have suggested its great importance without clearly defining a specific function: cyclic GMP is ubiquitously present in tissues of all animals tested (*5*); it is present in substantially higher concentrations in lung, brain, intestine, and thyroid tissues than were previously reported (*4, 6-8*); and substantially higher amounts of guanylate cyclase than were previously known have been found in the brain (*9*) and other organs (*10*). More recently, the cyclic nucleotide was linked to muscarinic cholinergic transmission in the central nervous system (*11*) and in the mammalian superior cervical ganglion of the peripheral nervous system (*12*). We now report the pharmacological effects of dibutyryl cyclic GMP in the central nervous system.

Male Sprague-Dawley rats were injected over a 90-second period with 15 μl (*13*) of either dibutyryl cyclic GMP (Sigma Chemical Co., 88.6 to 354.6 × 10^{-9} mole), morphine sulfate (13.5 to 78 × 10^{-9} mole), or saline vehicle in the lateral ventricle of the brain either by a freehand method (*14*) or through plastic cannulas stereotaxically implanted over one of the lateral ventricles, at least 1 week before testing.

Microinjections of 0.5 to 1 μl per site of either dibutyryl cyclic GMP (197 × 10^{-9} mole), morphine sulfate (13.5 to 78 × 10^{-9} mole), or saline vehicle at the rate of 1 μl over a 150-second period were administered to other groups of rats through bilateral cannulas stereotaxically implanted in the periaqueductal gray matter (PAG) (*15*) or the midbrain reticular formation (MRF) (*16*). Sites of injection or implantation were histologically confirmed at the time the animals were killed. All substances tested were prepared daily and not used thereafter.

Two blind observers separately recorded the rats' behavior before and after treatment. Five minutes before and 5 minutes after injection of dibutyryl cyclic GMP or saline vehicle analgesia was tested by tail pinch with a sharp towel clamp; the rats were then tested with a modified hot plate procedure (*17*). An identical protocol was followed for the rats treated with morphine, but to allow for the slower onset of action of the opiate, tests of analgesia were made 20 minutes after injection. Control and treated rats were tested for locomotor activity on an electronic activity monitor.

In naive rats or rats injected intracerebroventricularly with saline vehicle or 13.5 × 10^{-9} mole of morphine sulfate, tail clamping produced a loud squeak and instant struggle (Table 1). No rat of these groups tolerated gradient heat increases beyond 46.2° ± 1.14°C (Table 2). When the temperature exceeded 40°C, the rats exhibited a fairly constant sequence of behavioral alterations: diarrhea, hyperactivity, and alternate lifting of front paws.

Temperatures above 43°C produced frenzied hyperactivity with attempts to escape by lifting the cover of the hot plate apparatus. After vigorous and uninterrupted licking of front and rear paws, rats were removed from the hot plate (*18*).

Increasing doses of morphine (26 to 52 × 10^{-9} mole) decreased the responses to noxious stimuli (Table 1) but increased the severity of the symptoms associated with the opiate: loss of eyelid and corneal reflexes, sedation, depressed respiration, hypothermia, catalepsy, muscular rigidity, extension of limbs, or hyperreflexia. At 78 × 10^{-9} mole per rat, morphine totally abolished the responses to noxious stimuli but significantly increased the mortality rate. Naloxone (1.0 mg per kilogram of body weight) administered subcutaneously reversed within minutes all the actions of morphine.

Dibutyryl cyclic GMP, administered intracerebroventricularly, produced dose-related analgesia without sedation. At the higher doses of 354.6 to 394 × 10^{-9} mole per rat, dibutyryl cyclic GMP protected the rats against the pain of the deep penetration of the sharp points of the clamp into the tail. The squeak-struggle or freezing response, or both, were totally eliminated for 3 to 4 hours (Table 1). Most striking were the results obtained with the gradient hot plate procedure. Rats treated with 354.6 to 394 × 10^{-9} mole of dibutyryl cyclic GMP tolerated temperatures up to 60°C without any symptoms of hyperactivity or intolerance to heat. The experimental rats appeared calm and comfortable and resumed normal activity immediately after their removal from the hot plate. Despite their prolonged exposure to such high temperatures, none of the rats treated with dibutyryl cyclic GMP died. Rats treated with morphine (52 to 78 × 10^{-9} mole) also tolerated temperatures up to 60°C but were cataleptic, with rigidly extended limbs during and after the experiment. When exposed to temperatures above 54°C, these rats died within 1 to 4 hours (*19*).

Although morphine depressed locomotor activity for well over 4 hours, dibutyryl cyclic GMP did not alter the rats' activity (Table 1). Doses of dibutyryl cyclic GMP as high as 1 mg per rat (197 × 10^{-8} mole) produced no gross be-

havioral effects. Twenty-four hours after the injections, tail clamping and hot plate testing produced normal nociceptive responses, demonstrating total reversibility of the analgesic activity of the nucleotide. Naloxone (1.0 mg/kg) injected intravenously or subcutaneously neither prevented nor antagonized the analgesic effects of dibutyryl cyclic GMP. When administered intracerebroventricularly to rats addicted to morphine and abruptly withdrawn with naloxone (*20*), dibutyryl cyclic GMP (354.6×10^{-9} mole) did not suppress morphine withdrawal symptoms (*21*). Rats continuously infused for 72 hours with dibutyryl cyclic GMP (177.3×10^{-9} mole/hour) at the rate of 9 μl/hour did not exhibit any toxic symptoms or behavioral alterations. After cessation of the infusion neither spontaneously occurring nor naloxone-induced withdrawal symptoms were observed.

Microinjections of dibutyryl cyclic GMP (197 to 394×10^{-9} mole) into the PAG produced neither hyperactivity nor altered responses to noxious stimuli. Microinjections of morphine (52 to 78×10^{-9} mole) administered 2 days later to the same rats produced a full-blown hyperactive syndrome and analgesia (*15*). Microinjections of dibutyryl cyclic GMP into the MRF had no effect on behavioral activity and produced no analgesia; morphine microinjected into the same site produced tight head-to-tail rotations (*16*) and tail clamp analgesia.

The observation that the administration of dibutyryl cyclic GMP directly into the brain produced potent analgesic effects suggests that endogenous cyclic GMP is involved in the regulation of nociperception. While the molecular mechanism by which dibutyryl cyclic GMP inhibits the response to noxious stimuli is still undefined, our evidence from injection into three different brain sites that dibutyryl cyclic GMP does not mimic morphine suggests that the nucleotide and the opiate may not share a common mechanism of action. Dissimilarities of action between the opiate and the cyclic nucleotide are further suggested by the findings that in the guinea pig ileum bioassay, dibutyryl cyclic GMP produces dose-related contractions (*22*) while morphine inhibits the electrically stimulated contractions. Moreover, the failure of naloxone to reverse its analgesic activity strongly indicates that dibutyryl cyclic GMP does not bind to the opiate receptor.

All available evidence supports the hypothesis that analgesic effects are regulated by more than one mechanism and that inhibition of pain is mediated by more than one pathway (*23*). Nevertheless, a body of information is accumulating to suggest that cyclic GMP is involved in the analgesic processes. Recent studies in vitro have shown that enkephalin and morphine increase cyclic GMP levels in rat striatal slices (*24*). Morphine has also been reported to increase cyclic GMP concentrations in vivo in the rat neostriatum (*25*). Whether direct or indirect mechanisms are involved in the actions of morphine on cyclic GMP levels has not been established. Neither is it known which neurotransmitter system specifically mediates the effects of morphine on cyclic GMP concentrations in the diverse sites of the brain. For example, cerebellar concentrations of cyclic GMP were altered by drugs affecting cholinergic (*7*) and catecholaminergic (*8*) transmission. However, acetylcholine is one of the neurotransmitters implicated in the actions of both morphine (*26*) and cyclic GMP (*7*). But centrally administered acetylcholine possesses analgesic activity that is blocked by atropine (*27*), whereas atropine does not antagonize the analgesic properties of dibutyryl cyclic GMP (*28*). Likewise, iontophoretically applied atropine blocks the effects of acetylcholine but not those of cyclic GMP (*7*).

Table 2. Comparison of tolerance to heat stimuli after injection of morphine and dibutyryl cyclic GMP in a volume of 15 μl into a lateral ventricle. We modified the hot plate constant-temperature method (*17*) by using gradually increased temperatures. Rats were placed on the hot plate at room temperature (20° to 21°C) for at least 5 minutes after injection of dibutyryl cyclic GMP, and for 20 minutes after injection of morphine sulfate. The temperature was then gradually increased at a constant rate of 2.77°C per minute until the rats showed nociceptive responses, manifested by vigorous paw licking and rearing. With this method it is possible to reliably and reproducibly quantitate the dose-related antinociceptive activity of a substance and determine the temperature tolerance differential between treatment groups. Doses of morphine sulfate and dibutyryl cyclic GMP are expressed as nanomoles of morphine and cyclic GMP, respectively. Each value represents the mean ± standard deviation in a group of ten rats.

Treatment	Dose (nmole)	Mean temperature (°C)
Morphine sulfate	13.5	45.1 ± 1.52
	26	46.4 ± 1.58
	52	54.7 ± 3.77*
	78	57.4 ± 2.46*
Dibutyryl cyclic GMP	88.6	44.7 ± 1.42
	118.2	45.9 ± 1.66
	147.8	51.8 ± 3.29*
	177.3	56.1 ± 3.38*
	354.6	58.1 ± 1.97*
Saline vehicle		46.2 ± 1.14

*$P < .05$; Tukey test for multiple comparisons.

In summary, although we have not yet identified the sites of action of the cyclic nucleotide, dibutyryl cyclic GMP mediates analgesia along a pain-inhibitory pathway that may be different from that of the opiates. Of considerable potential are our findings that the analgesic properties of dibutyryl cyclic GMP were totally dissociated from the centrally depressant effects of the opiates and opiate-like peptides and that dibutyryl cyclic GMP–treated rats survived burn trauma that was fatal to morphine-treated rats.

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19. Rats exposed to temperatures above 54°C were protected against noxious stimuli by effective analgesic treatment. Similarly, morphine-treated rats that died within 1 to 4 hours did so before cessation of the analgesic activity of morphine. We have throughout followed the guide-

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Precocious Cardiac Orienting in a Human Anencephalic Infant

Abstract. *An anencephalic infant, 3 to 6 weeks old, responded to acoustic stimulation with cardiac decelerations typical of the response pattern seen in normal, older infants. Such precocity implies unexpected competence of lower brain structures and suggests that, in the normal infant, feedback from immature higher centers may sometimes interfere with rather than modulate the functioning of lower centers.*

Slowing of heart rate following sensory stimulation presumably reflects attention or orienting to stimuli that carry information (*1, 2*). The slowing response is difficult to elicit during sleep (*3*) or from human infants less than about 2 months of age, but it is easily evoked from awake older infants (*4–6*). It is one of a number of qualitative changes in behavior which suggest that 2 months marks the period at which cortical-subcortical circuits become functional (*5, 7*).

Anencephalic infants would not, therefore, be expected to show the cardiac-orienting response. Although Brackbill (*8*) used the term "orienting reflex" to describe white noise–elicited behavioral changes observed in a 3-month-old anencephalic infant, the observed behaviors included startles and activity increases that are usually associated with cardiac acceleration. Recently, we studied a 4½-month-old hydr*an*encephalic infant and were surprised to find that acoustic stimuli evoked reliable cardiac slowing of characteristic latency, form, and duration which was frequently accompanied by behavioral quieting, eye widening, and sucking cessation. We could not verify morphological characteristics of the brain but tentatively assumed that basal ganglia and diencephalon might have developed at near-normal rates (*9*) and were capable of organizing the age-appropriate response.

Subsequently, we studied an anencephalic infant at ages 19, 20, 25, and 40 days. The infant died at 51 days, and autopsy showed a skull defect and a severely hypoplastic brain, weighing only 39 g. (The brain of a normal newborn weighs approximately 350 g.) Minute cerebral hemispheres with poorly developed lobation could be identified; but the diencephalon was absent, and cerebral microscopic as well as gross structure was so distorted as to preclude function. Molecular and neuronal layers varied irregularly in thickness, displaced gray matter was embedded in the white matter, and there were focal areas of calcification. The midbrain was also severely malformed; only lower levels of the brain, including medulla, pons, and cerebellum, were grossly normal though underdeveloped.

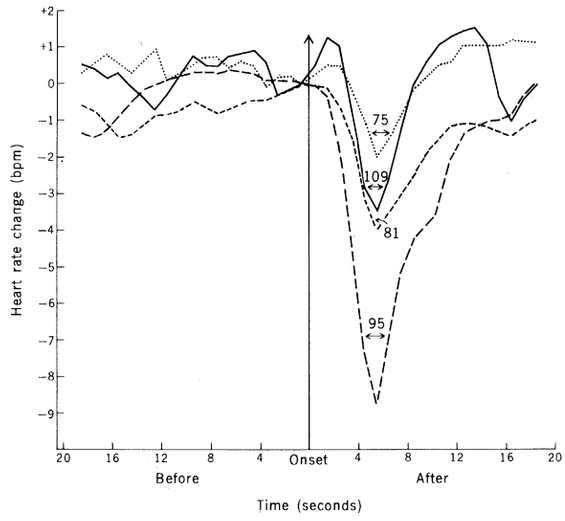

Fig. 1. Heart rate change for 19 seconds preceding and following the onset of acoustic stimuli of varying intensity (*14*).

Like the hydranencephalic infant, this infant also responded to acoustic stimulation with cardiac slowing. Tactile, olfactory, and mock stimuli did not produce reliable heart rate change, and visual stimuli were not tested. (Pupillary light reflexes were absent.) Over four 2- to 3-hour sessions, we presented 452 stimulations of which 330 were sounds with a 30-msec rise time, an intensity between 75 and 109 db (referred to a sound pressure of 20 micronewtons per square meter), and a duration of five or more seconds. The sounds included (i) continuous, constant-frequency sine waves at 250, 1000, 1800, and 6000 hertz; (ii) constant-frequency sine waves pulsed at various on : off ratios; (iii) frequency-modulated (FM) triangular waves sweeping at different rates to produce warbles or trills; (iv) trains of three-format, synthetic speech syllables, [ba] and [ga] (*6*); and (v) broadband white noise. The five classes of sound stimuli were presented in sets of varying numbers of trials, interspersed among tactile and olfactory sets. No successive sets were drawn from the same class of stimuli, and the order of sets was approximately balanced across sessions. Within sets, intertrial intervals averaged 36.4 seconds (standard deviation, 9.5 seconds). The interval between sets varied from 90 seconds to several minutes.

Testing was carried out in a sound-attenuated chamber with the infant reclining on a padded seat; stimulus-generating, calibrating, timing, and recording equipment were located outside the chamber (*6*). Chest electrodes detected cardiac R waves whose interbeat intervals were computer digitized and converted to heart rate (in beats per minute) for each second for 19 seconds preceding and 19 seconds following stimulus onset. Other activities recorded were respiration (via a mercury strain-gauge, session 4), electromyographic response of orbicularis oculi (not reported here), and sucking (which was too weak to provide satisfactory records). Sounds were delivered either through a midline speaker or through an earphone (modified Grason-Stadler TDH-49) held in place by a staff member. A pediatrician and a second staff member remained in the chamber to monitor the infant's condition and to rate behavior. Throughout, the infant

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