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The Function of Lateral Hypothalamic Catecholamine and Endorphin Systems in the Control of Motor Performance

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WILLIS, G. L. *The function of lateral hypothalamic catecholamine and endorphin systems in the control of motor performance.* PHARMACOL BIOCHEM BEHAV **28**(2) 197–202, 1987.—Morphine (1 or 10 μg in 1 μl) or β-endorphin (1 μg in 1 μl) were injected bilaterally into the posterior lateral hypothalamus of Sprague-Dawley rats to determine what effect they may have on motor performance. Severe reductions in open field performance and motor reflex control were observed after the injection of 1 μg of β-endorphin or morphine into this area. The injection of 10 μg of morphine into the same area was less effective in causing motor impairment. The central (32.7 μg in 1 μl) and peripheral (2 mg/kg) injection of naloxone did not prevent the motor impairment observed after the injection of β-endorphin or morphine. Pretreatment with 6-hydroxydopamine into the lateral hypothalamus in a multistage regime did not prevent the motor impairment observed after β-endorphin or morphine injection. These results indicate that lateral hypothalamic participation in the control of motor function may not involve the ascending nigrostriatal and mesocortical dopamine systems and that endogenous opiate systems may function independently to influence motor performance.

Morphine β-Endorphin Lateral hypothalamus Catecholamines Naloxone 6-Hydroxydopamine

IT has been suggested that the ascending dopamine (DA) and endorphinergic (βEP) systems in mammalian CNS are important in the physiological regulation of motor function and appetite [6, 10, 11, 18, 31, 32, 34, 35]. The involvement of DA has been most convincingly demonstrated in studies in which nigrostriatal and mesolimbic DA are depleted from various terminal fields which results in the impairment of motor function and consummatory behaviour [31,32]. These behaviours can be restored if DA agonists are injected into a body compartment which will permit access to receptors adjacent to the depleted DA terminal fields [5,15].

The participation of βEP-ergic systems in motor and appetitive responses has also been studied extensively. While central and peripheral injection of βEP can alter appetite [18, 19, 24], increased concentrations of this endogenous opiate have been detected in the blood of genetically obese mice and obese humans and in experimental animals undergoing various schedules of food deprivation [7, 16, 19]. In addition, βEP-ergic control of motor function has been postulated on the basis of experiments demonstrating that intraventricular and intracerebral injections of this peptide can precipitate abnormal motor responses in experimental animals [19,22].

In our previous work, we have defined the temporal, morphological and pharmacological characteristics of amine accumulation in the degenerating proximal axons of ascending aminergic neurones as they traverse the lateral hypothalamus (LH) [31,32]. We hypothesize that this accumulation may represent pools of functional amine which affect a specific subpopulation of catecholamine (CA) receptors to cofunction with terminal depletion, to yield the spectrum of behavioural deficits which characterise the DA-depleted animal [3,14]. Furthermore, we have shown that several CA agonists, which produce amine accumulation, can also produce DA degeneration associated behavioural deficits, without producing terminal amine loss [29, 30, 33].

In consideration of the CA agonistic properties which morphine and βEP possess [4, 8, 9, 12, 21] it was the object of the present study to determine whether the injection of these substances, directly into the hypothalamus where amine accumulation occurs, may produce deficits in motor function similar to those seen after DA depleting lesions. Such injections may activate endogenous βEP systems which have been hypothesised to cofunction with CA to control various aspects of behaviour [17].

METHOD

Eighty-four male Sprague-Dawley rats weighing approximately 200 g were housed in plastic boxes with wire tops in a room in which the light/dark cycle was 12 hr on/off with lights on at 0800 hr. The temperature was maintained at 22°C (±2°C).

TABLE 1

TYPE, DOSE AND ROUTE OF ADMINISTRATION OF DRUGS EMPLOYED TO DETERMINE THEIR EFFECT ON MOTOR PERFORMANCE

Group	Control Injection	Test
1	1 μl saline	1 μl of 1 μg/μl βEP
2	1 μl saline	1 μl of 1 μg/μl morphine
3	1 μl saline	1 μl of 10 μg/μl morphine
4	1 μl saline and 1 μl of 1 μg/μl βEP	1 μl of 32.7 μg/μl naloxone and 1 μl of 1 μg/μl βEP
5	1 μl saline and 1 μl of 1 μg/μl morphine	1 μl of 32.7 μg/μl naloxone and 1 μl of 1 μg/μl morphine
6	multistage 6-OHDA and 1 μl saline	multistage 6-OHDA and 1 μl of 1 μg/μl βEP
7	multistage 6-OHDA and 1 μl saline	multistage 6-OHDA and 1 μl of 1 μg/μl morphine
8	1 ml/kg SC saline and 1 μg/μl βEP	2 mg/kg SC naloxone and 1 μl of 1 μg/μl βEP
9	1 ml/kg SC saline and 1 μg/μl morphine	2 mg/kg SC naloxone and 1 μl of 1 μg/μl morphine

All injections were central unless otherwise stated.

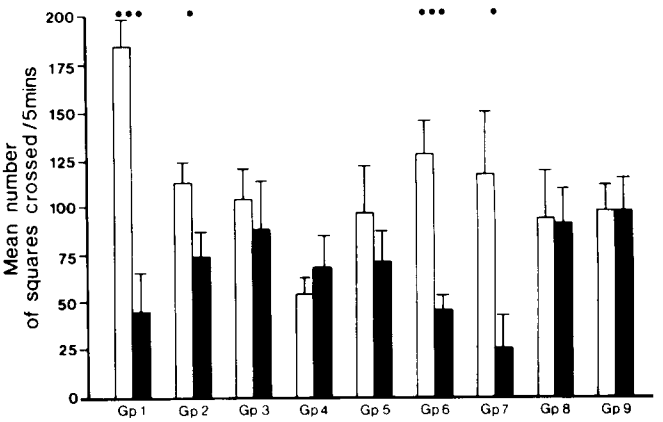

FIG. 1. The mean number of squares crossed during a 5 min exposure to an open field. The animals represented by the open bars in groups 1–3 received intracerebral injections of vehicle while the filled bars in these groups represent the performance of animals injected with 1 μg of βEP, 1 μg and 10 μg of morphine sulphate respectively. For groups 4 and 5 respectively, the control animals (open bars) were injected with vehicle before receiving 1 μg of βEP or morphine, while the closed bars represent those which were treated with naloxone before the injection of βEP or morphine. The closed bars for groups 6 and 7 represent those animals injected with 6-OHDA in a multistage regime before receiving 1 μg βEP (group 6) or 1 μg morphine (group 7) into the hypothalamus. The open bars in these 2 groups represent 6-OHDA treated animals receiving saline. The animals represented in groups 8 and 9 are those injected with SC naloxone (2 mg/kg) immediately before receiving 1 μg of βEP or morphine before the test session. The open bars in those groups represent animals treated with βEP or morphine but without naloxone pretreatment. The T-bars represent the standard error of the mean and the number of dots represent the level of significance. 1=$p<0.05$; 2=$p<0.01$; 3=$p<0.005$.

Surgery

Animals were anaesthetised with 84 mg/kg of alphaxalon (Glaxo; Victoria, Australia) and then placed in a stereotaxic instrument. Bilateral cannulae were implanted just dorsal to the LH at the coordinates (A=−1.6 mm, L=±1.9 mm and D=−6.1 mm). The injection needle extended 2 mm beyond the cannula tip. All coordinates given were relative to bregma and were in the plane of Pellegrino *et al.* [20].

Injections and Solutions

The following solutions were used in the study. β-Endorphin (camel) (Sigma; USA) was mixed in the concentration of 1 μg/μl for central injection. Naloxone hydrochloride (Narcan; Endo Laboratory, Sydney, Australia) was mixed in concentration of 32.7 μg in 1 μl for central injection and 2 mg/ml for peripheral (SC) injection. Morphine (David Bull; Melbourne, Australia) was mixed in the concentrations of 1 μg/μl and 10 μg/μl for central injection only. All drugs injected centrally were administered bilaterally in a volume of 1 μl and SC injections were made in a volume of 1 ml/kg. Isotonic saline was the vehicle which was used for making central injections. 6-Hydroxydopamine hydrobromide (6-OHDA; Sigma, USA) was mixed in a concentration of 8 μg/μl and was injected in a volume of 2 μl in a special regime as described below. Control injections for this procedure were made with saline/ascorbic acid vehicle which is employed to prevent the rapid oxidation of 6-OHDA [27]. New solutions of all drugs were prepared immediately prior to injection and unused portions were discarded at the end of each session.

Behavioural Tests

Five behavioural tests were employed in the present study to measure various aspects of motor function. Open field behaviour was measured by placing each animal in a PVC box fitted with infrared sensors which detect horizontal (number of squares crossed) and vertical (number of rearings onto the hind limbs) during a 5 min test period. The mean number of responses and activity plots were generated by a computer and displayed on a monitor at the end of each 5 min session. Three tests were employed to assess motor function directly after the completion of the open field activity assessment: Latency to retract an elevated limb, latency to step down from a raised platform and latency to step from within a prescribed area, similar to tests which have been used routinely to assess motor function previously [1, 30, 33].

Procedure

There were nine groups of rats employed in this study. Each animal served as its own control on a crossover design. On day 1 half of the animals in each group would receive a control injection while the others served as the experimental group. On the day after this, the control and experimental conditions were reversed for the same animals. Two groups of animals (groups 6 and 7) received multistage 6-OHDA lesions for 8 weeks before receiving intrahypothalamic βEP or morphine. This procedure requires that the 6-OHDA be injected gradually over a long time period in order to avoid the acute effects which may incapacitate the animal. However, severe depletion of various forebrain CA systems still occurs [28]. For a thorough description of the various treatment groups which were employed in the study refer to Table 1. All drug injections were made immediately prior to

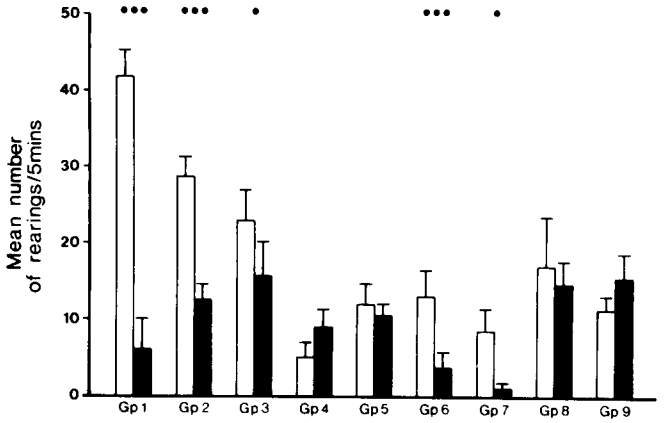

FIG. 2. The mean number of rearings onto the hind feet during a 5 min exposure to the open field. The doses of βEP, morphine, naloxone or 6-OHDA treatment employed for each of the groups are expressed in Fig. 1 and Table 1. The animals represented by the open bars in groups 1–3 received intracerebral injections of vehicle while the filled bars in these groups represent the performance of animals injected with 1 μg of βEP, 1 μg and 10 μg of morphine sulphate respectively. For groups 4 and 5 respectively, the control animals (open bars) were injected with vehicle before receiving 1 μg of βEP or morphine, while the closed bars represent those which were treated with naloxone before the injection of βEP or morphine. The closed bars for groups 6 and 7 represent those animals injected with 6-OHDA in a multistage regime before receiving 1 μg βEP (group 6) or 1 μg morphine (group 7) into the hypothalamus. The open bars in these 2 groups represent 6-OHDA treated animals receiving saline. The animals represented in groups 8 and 9 are those injected with SC naloxone (2 mg/kg) immediately before receiving 1 μg of βEP or morphine before the test session. The open bars in those groups represent animals treated with βEP or morphine but without naloxone pretreatment. The T-bars represent the standard error of the mean and the number of dots represent the level of significance. 1=$p<0.05$; 2=$p<0.01$; 3=$p<0.005$.

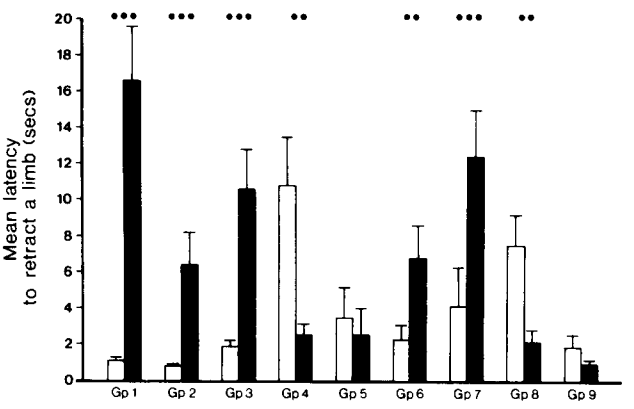

FIG. 3. The mean latency to retract an elevated forepaw for rats treated with βEP, morphine, naloxone or 6-OHDA. The animals represented by the open bars in groups 1–3 received intracerebral injections of vehicle while the filled bars in these groups represent the performance of animals injected with 1 μg of βEP, 1 μg and 10 μg of morphine sulphate respectively. For groups 4 and 5 respectively, the control animals (open bars) were injected with vehicle before receiving 1 μg of βEP or morphine, while the closed bars represent those which were treated with naloxone before the injection of βEP or morphine. The closed bars for groups 6 and 7 represent those animals injected with 6-OHDA in a multistage regime before receiving 1 μg βEP (group 6) or 1 μg morphine (group 7) into the hypothalamus. The open bars in these 2 groups represent 6-OHDA treated animals receiving saline. The animals represented in groups 8 and 9 are those injected with SC naloxone (2 mg/kg) immediately before receiving 1 μg of βEP or morphine before the test session. The open bars in those groups represent animals treated with βEP or morphine but without naloxone pretreatment. The T-bars represent the standard error of the mean and the number of dots represent the level of significance. 1=$p<0.05$; 2=$p<0.01$; 3=$p<0.005$.

placing the animal in the open field chamber. After the completion of the behavioural tests, all animals were rapidly decapitated and their brains stored in 10% buffered formaldehyde. The brains were later sectioned at 50 μm with a vibratome, placed on glass slides and then stained with cresyl violet and luxol fast blue. Areas of damage resulting from cannulation and injection were plotted on plates extracted from Pellegrino *et al.* [20]. Paired *t*-tests were used to analyse the data by using a Canon BX-10 statistical package.

RESULTS

As shown in Fig. 1, the injection of 1 μg of βEP into the LH caused a significant reduction in the number of squares crossed during a 5 min test, when compared to their respective control performance ($p<0.005$). The injection of 1, but not 10 μg of morphine into the LH also produced a significant decrease in the number of squares crossed ($p<0.05$). The bars representing groups 4 and 5 reveal that the injection of 32.7 μg of naloxone into the LH, directly before βEP or morphine injection, did not block the opiate induced motor inhibition which these drugs produced. The traces for groups 6 and 7 reveal that previous CA depletion of various CA systems with multistage 6-OHDA injection did not prevent the inhibition of βEP or morphine induced motor impairment as both were significant from control performance ($p<0.005$ and $p<0.05$ respectively). Results for groups 8 and 9 reveal that pretreatment with 2 mg/kg of naloxone (SC) also failed to block the impairment of locomotion produced by central injections of 1 μg of morphine or βEP.

As shown in Fig. 2, the number of rearings in an open field was similarly affected in the various treatment groups. A severe reduction in rearings was observed after the intrahypothalamic injection of βEP or 1 μg of morphine, while a slight but significant reduction in this parameter was seen after the injection of 10 μg of morphine ($p<0.005$, 0.005 and 0.05 respectively for groups 1, 2 and 3). The injection of naloxone into the LH immediately before βEP or morphine (groups 4 and 5) did not block this response while depletion with multistage injections of 6-OHDA (groups 6 and 7) did not alter the morphine or βEP induced response. As with locomotion, peripheral injection of naloxone (groups 8 and 9) failed to block the effect of central βEP and morphine.

The injection of 1 μg of βEP and 1 or 10 μg of morphine caused a significant increase in the latency to perform the limb retraction and step down and ambulation tests ($p<0.05$ in all cases; Figs. 3, 4 and 5). Only on the latency to ambulate test was the 10 μg dose of morphine without effect. For groups 4 and 5 on all tests, except latency to retract a limb, the central injection of naloxone immediately prior to intrahypothalamic βEP or morphine did not successfully block the effect of these opiates. The performance of these naloxone pretreated βEP injected animals improved significantly compared to that of βEP injected animals pretreated

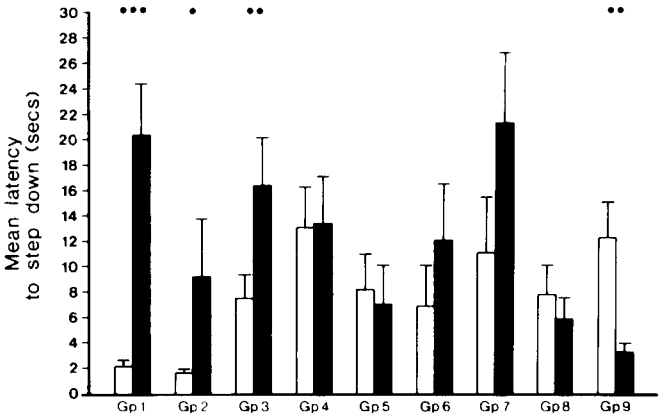

FIG. 4. The mean latency to step down from a raised platform for rats treated with βEP, morphine, naloxone or 6-OHDA. The animals represented by the open bars in groups 1–3 received intracerebral injections of vehicle while the filled bars in these groups represent the performance of animals injected with 1 μg of βEP, 1 μg and 10 μg of morphine sulphate respectively. For groups 4 and 5 respectively, the control animals (open bars) were injected with vehicle before receiving 1 μg of βEP or morphine, while the closed bars represent those which were treated with naloxone before the injection of βEP or morphine. The closed bars for groups 6 and 7 represent those animals injected with 6-OHDA in a multistage regime before receiving 1 μg βEP (group 6) or 1 μg morphine (group 7) into the hypothalamus. The open bars for these 2 groups represent 6-OHDA treated animals receiving saline. The animals represented in groups 8 and 9 are those injected with SC naloxone (2 mg/kg) immediately before receiving 1 μg of βEP or morphine before the test session. The open bars in those groups represent animals treated with βEP or morphine but without naloxone pretreatment. The T-bars represent the standard error of the mean and the number of dots represent the level of significance. 1=$p<0.05$; 2=$p<0.01$; 3=$p<0.005$.

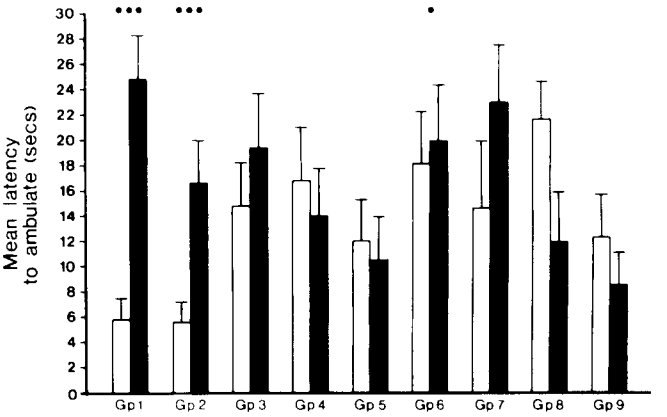

FIG. 5. The mean latency to ambulate from within a prescribed area for rats treated with βEP, morphine, naloxone and 6-OHDA. The animals represented by the open bars in groups 1–3 received intracerebral injections of vehicle while the filled bars in these groups represent the performance of animals injected with 1 μg of βEP, 1 μg and 10 μg of morphine sulphate respectively. For groups 4 and 5 respectively, the control animals (open bars) were injected with vehicle before receiving 1 μg of βEP or morphine, while the closed bars represent those which were treated with naloxone before the injection of βEP or morphine. The closed bars for groups 6 and 7 represent those animals injected with 6-OHDA in a multistage regime before receiving 1 μg βEP (group 6) or 1 μg morphine (group 7) into the hypothalamus. The open bars for these 2 groups represent 6-OHDA treated animals receiving saline. The animals represented in groups 8 and 9 are those injected with SC naloxone (2 mg/kg) immediately before receiving 1 μg of βEP or morphine before the test session. The open bars in those groups represent animals treated with βEP or morphine but without naloxone pretreatment. The T-bars represent the standard error of the mean and the number of dots represent the level of significance. 1=$p<0.05$; 2=$p<0.01$; 3=$p<0.005$.

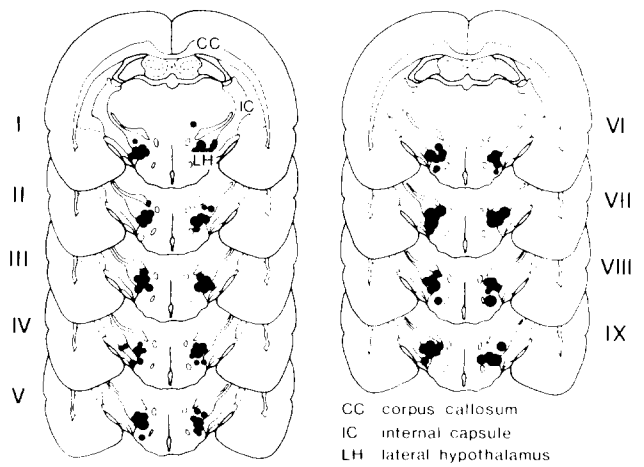

FIG. 6. Representative plates (20) depicting the placement of cannulae tips in animals injected with βEP, morphine, naloxone or 6-OHDA. The type and dose of substance injected for each respective group is expressed in Table 1 and Fig. 1.

with vehicle ($p<0.01$). The latency to retract a limb response in multistage 6-OHDA depleted animals after intrahypothalamic morphine or βEP was not attenuated by this pretreatment regime. On the latency to step down test, the multistage treated animals behaved as they did on control days while only the animals receiving intrahypothalamic morphine showed attenuation of the morphine-induced ambulation deficits after the multistage regime. The peripheral injection of naloxone blocked the morphine-induced motor impairment but did not affect performance on the latency to step down in morphine injected animals treated with peripheral naloxone.

As shown in Fig. 6, the cannulations allowed repeated placement of the injection needle in close proximity to the LH.

DISCUSSION

These results demonstrate that the injection of βEP or morphine into the LH can produce an impairment of motor function similar to that observed after 6-OHDA injection or after the administration of various CA agonists [31,32]. The site of injection in the LH was chosen specifically because this is where amines accumulate in the axons of degenerating CA neurones, after the central injection of 6-OHDA [32]. As with 6-OHDA, increased synthesis and release of amines caused by this exogenous βEP or morphine is similar to that produced endogenously by 6-OHDA or lesions to the same area and we would predict that the behavioural deficits occurring after 6-OHDA or agonist treatments would be similar. While the effects of reduced appetite have been reliably observed after the administration of CA agonists into

the perifornical region of the hypothalamus [2, 3, 14, 31, 32], we extend this to include motor performance impairment after the administration of such compounds into this brain region. Such a finding is consistent with the hypothesis that the amines which accumulate in the axons of degenerating medial forebrain bundle neurones are neuroactive and that they affect a subpopulation of CA receptors involved in the control of motor function and consummatory behaviour. That many of the consummatory and motor deficits seen after DA-depleting lesions can be produced by injecting agonists into the LH lends indirect support to the contention that amine accumulation may participate in the production of behavioural deficits attributed previously to the loss of functional transmitter in the terminal fields [32].

This contention is supported further by the finding that even though the amine content of the striatum, accumbens nucleus and olfactory tubercle can be severely reduced by a 6-OHDA treatment regime similar to the one employed in the present study ([28]; groups 6 and 7), severe impairment of motor function in response to βEP or morphine injection was still observed. However, due to the limited diffusion of 6-OHDA, hypothalamic systems probably remained intact. While such an injection regime avoids the formation of endogenous amine accumulation, at the site of βEP and morphine injection in the LH, the motor impairment which these opiates produced still occurred in the presence of such forebrain depletion. We therefore conclude that the role of hypothalamic CA systems in the control of motor function may be independent of that exerted by the ascending nigrostriatal and mesocortical CA systems.

We conclude that morphine and βEP systems still caused severe decrements in motor performance via activation of hypothalamic CA systems in the presence or absence of ascending CA systems. It is also possible that this morphine or βEP-induced motor impairment may be mediated by endogenous opioid systems which function independently of central CA systems. This is supported by the finding that βEP and morphine induced motor impairment was observed in animals pretreated with the multistage injection of 6-OHDA. Whether or not the endogenous opioid systems function independently of the central CA systems could account for the difference between catatonia and neuroleptic-induced catalepsy [23,26]. Whether these two states are qualitatively different is an issue which is yet to be resolved.

Findings from the present study, which are difficult to interpret, are the failure of centrally and peripherally administered naloxone to block the inhibitory effects of βEP or morphine. In consideration of the numerous reports which demonstrate the antagonism of opiate and opioid effects by doses of naloxone similar to those used in the present study (i.e., [4,34]), we predicted that naloxone would prevent the occurrence of the observed effects. It is possible that a "carry over" effect which is inherent in a crossover design, cancelled out the expected recovery of motor function. This, however, must be an unique characteristic of the combined treatments, since the effect of βEP and morphine, alone, caused severe reductions in motor performance, despite the fact that a crossover design was used.

Other variables including the dose of opiates employed, the site of injection and the time of behavioural testing all deserve consideration when interpreting the present results. It has been shown that the injection of βEP into the CSF of experimental animals has a biphasic effect [22,25]. An initial period of behavioural depression is followed by behavioural activation. The duration of such an effect is also dose dependent. While the time of observation in the present study would be during the initial phase of behavioural depression, the two doses of morphine employed confirm the finding that the initial periods of depression can be decreased if the dose of opiate is increased [22,25]. While this period of behavioural activation was not studied in detail in the present study, the period of motor impairment corresponds well with the time required for increased CA synthesis and release to occur after opiate administration [3, 4, 8, 9, 12, 21]. The observed effects after injection into the LH have not been reported previously [22, 25, 26]. The most robust behavioural consequences of βEP injection have been reported after injections into the periaqueductal grey [22,26]. While such a finding is consistent with the neurochemical work describing the distribution of βEP systems within mammalian brain [13], LH-βEP systems have been hypothesised to be important in the control of various behaviours [17]. It is the object of the present paper to point out that the role of LH-βEP systems in the control of motor function may be more important than has been previously recognised.

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