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Separate and Combined Effects of Morphine and Amphetamine on Quantitative Electroencephalogram and Regional Cerebral Glucose Uptake in a Rat Model

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Abstract. The effects of morphine (5 mg/kg) and amphetamine (5 mg/kg) were examined on relative regional cerebral glucose uptake (RrCGlu), surveyed in 20 brain areas in the rat. No relationship was found between drug effects on the cortical RrCGlu and the quantitative electroencephalogram (QEEG) measured from frontal and occipitoparietal cortices. Discriminant function analysis revealed that the two drugs produced identifiably different QEEG changes and that the combination engendered an unique metastate that most closely resembled amphetamine's effect with no morphine characteristics. The two drugs evoked qualitatively similar RrCGlu changes at most sites surveyed, with certain exceptions which are discussed. Both increased RrCGlu at the substantia nigra. Morphine, but not amphetamine, increased RrCGlu at the periaquaeductal gray. Since amphetamine is known to potentiate morphine analgesia and to ameliorate many of the opiate's depressant effects, the finding that the combination evokes cortical QEEG changes that more closely resemble amphetamine may have implications for understanding the increased psychotoxicity of chronic combined abuse.

Introduction

The coadministration of opiate and sympathomimetic, psychostimulant, drugs is common to both analgesic therapy and illicit drug abuse; yet few studies have been conducted to examine the neurophysiological consequences of their interaction. In the clinical setting, sympathomimetics such as cocaine or *D*-amphetamine have historically been added to opiate analgesic regimens in the preparation of 'Brompton cocktail'-type medications for the treatment of severe malignant pain.

The rationale for therapeutic coadministration of opiates and sympathomimetics is based upon the early clinical research of Ivy et al. [1] who demonstrated that the acute combination enhanced the analgesic effect of morphine on experimental pain in humans. Later studies confirmed these findings in various clinical pain states and laboratory animals. They provided evidence that the undesirable effects of morphine including respiratory depression, nausea, and sedation are mitigated or relieved by *d*-amphetamine even while analgesia is enhanced [2–7].

In the sphere of illicit drug use where polydrug dependencies are the rule rather than the exception [8], opiates are frequently combined with sympathomimetic drugs of which class *d*-amphetamine is the prototype. The combination is known as a 'speedball' in illicit circles [9].

The precise mechanisms through which morphine and *d*-amphetamine interact have not been fully explored. Amphetamine and other sympathomimetics are known to elevate synaptic levels of monoamines from catecholaminergic and serotoninergic neurons within the central nervous system, neurotransmitters which sub-

serve the central effects of opiates: noradrenaline [10], dopamine [11, 12], and serotonin [13, 14].

In its illicit usage, amphetamine was first reported as an adjunct to intravenous opiate abuse in the early 1950s [9] where it replaced cocaine in the earlier cocaine-heroin form of the 'speedball'. Sympathomimetics are coadministered with opiates by the illicit user to ameliorate some of the depressant effects of the opiate and subjectively to enhance other effects such as euphoria and analgesia.

A proposal recently advanced by Wise and Bozarth [15] may provide a biological basis for the greater addictiveness of the amphetamine-morphine combination than either of the two agents alone. These authors have found that morphine acts to induce reward by an effect at the ventral tegmentum of the mesolimbic system, amphetamine sustains its rewarding effects by an action at the nucleus accumbens, and these two different reward systems are both 'wired' apparently in series in a common 'reward pathway' in the brain. Evidence for these two agents acting through a common reward mechanism has recently been provided by Stewart and Vezina [16] who report that rats trained to self-administer intravenous heroin and in whom this behavior has been extinguished, will reinstate self-administration, if either morphine is injected to the ventral tegmentum or if amphetamine is microinjected to the nucleus accumbens.

It is our common clinical experience that the illicit practice of chronic combined opiate-amphetamine coadministration leads to a complex codependence with prominent psychotomimetic features of the amphetamine type. Thus, it seems worthwhile to study the acute and chronic interactions of these drugs in order to ascertain the similarity and differences of the combined intoxication to the states produced by the individual agents themselves.

The present study was undertaken to examine the acute effects of these drugs, and of their interaction, on the quantitative electroencephalogram (QEEG), a method that is amenable to discriminant function analysis for identification of similarities and differences in cortical electrophysiological effects [17]. In addition, recent studies revealing a close association between the QEEG and cerebral metabolism – measured by positron emission tomography – in humans [18] prompted us to survey the regional cerebral glucose uptake (rCGlu) capacity (or rate) in the rat brain under the influence of morphine and amphetamine associated with defined QEEG states.

Materials and Methods

Animals

Fifty-nine male Sprague-Dawley rats (200–250 g) were used in these studies, purchased from Sasco laboratories. Animal housing and experimental facilities employed identical temperature (20 ± 0.5 °C) and humidity (40 ± 5%) control with 12-hour light-dark rhythm. The animals were acclimated to local conditions for 1 week prior to surgical implantation of chronic extradural silver ball electrodes. Twenty animals were assigned to rCGlu studies (morphine, n = 6; amphetamine, n = 6; control, n = 8) and 39 to QEEG studies (morphine, n = 13; amphetamine, n = 5; both drugs, n = 8; control, n = 13).

Electrode Implantation

Under pentobarbitone anesthesia (50–60 mg/kg i.p.) the animal's head is restrained stereotaxically, the skin overlying the skull incised midsagittally, then undermined and retracted. The periosteum is cleared and five burr holes (1.0 mm) are made bilaterally, overlying occipitoparietal and frontal cortices (sagittal ± 4.0 mm, lamboidal + 1 mm *and* sagittal ± 3, interorbital – 1.0 mm, respectively). A fifth reference burr hole is made overlying the nasion anterior to the interorbital suture. The electrodes are then inserted through their holes to lie epidurally, the holes sealed with sterile bone wax and the entire array embedded in dental acrylic, anchored to the skull by means of four stainless steel screws embedded in the bone [19].

Jugular Catheter Implantation

Fourteen days were permitted to elapse before jugular catheters were surgically implanted under light halothane anesthesia according to the method of Lipman and Tolchard [20], the catheter being tunneled subcutaneously to the acrylic mantle at the skull, filled with heparinized (10 U/ml) saline, and capped. This preparation was allowed to recover for 1 week prior to drug administration and regional cerebral glucose administration or QEEG measurement.

QEEG Measurements

The apparatus and method used for QEEG measurement have been previously described [19, 21]. Briefly, the animals were placed in individual clear acrylic observation chambers (30 × 30 × 60 cm) in which they were permitted to roam freely and acclimate after their electrodes had been attached to the QEEG measuring apparatus by light flexible tethers. Drugs were then administered as described below and animals observed for behavior for 15 min, after which two 100-second QEEG epochs were sequentially sampled. Signals were amplified by means of an EEG machine (Grass, model 89) and the amplified signals digitally sampled in the range 0–20 Hz by means of a microcomputer (IBM PC/XT) program developed in this laboratory [21]. QEEGs were estimated from 5 animals administered amphetamine, 13 administered morphine, 8 administered both drugs, and 13 administered saline (control).

Statistical Analysis of QEEG Signals

Digitized signals (0–20 Hz) were analyzed on-line, as they were acquired, by fast Fourier transformation in 4-second epochs into the frequency domain. Spectral data so derived were then subjected to further statistical analysis at a remote mainframe computer (DEC VAX) using the F distribution based multivariate analysis and stepwise discriminant function analysis programmes of a commercial statistical analytic package (BMDP).

rCGlu Measurements

The method of rCGlu measurement has been described in more detail elsewhere [20]. Briefly, 15 min after drug injection, the rats were administered a 40-μCi pulse of ^{14}C-2-deoxy-*D*-glucose (^{14}C-2DG) in 0.9% saline (Pathfinder Laboratories) via the jugular catheter and 45 min permitted to elapse before sacrifice. The majority of the ^{14}C-2DG elutes from blood to tissue within the first 5 min, as judged by sequential venous sampling. The animals were sacrificed by exsanguination during the perfusion-fixation process under light halothane anesthesia and brains perfusion-fixed in situ prior to removal and further (5 days) fixation in phosphate-buffered formalin (10%, pH 7.0). The brain was then sliced in 1.0-mm coronal sections and the tissue sampled directly by the punch technique prior to processing, digestion, and scintillation counting for ^{14}C-2DG estimation. Statistical analysis of normalized data was conducted by using the Mann-Whitney U test [22].

Calculation of Relataive rCGlu (RrCGlu)

Calculation of RrCGlu was then accomplished by computing the entire ^{14}C dpm/mg (wet weight) in the brain as a whole and expressing each sample dpm/mg as a fractional percentage of the whole brain total according to the method of Delanoy and Dunn [23]. This value is thus relative and dimensionless and expresses the fractional accumulation of tracer in each region of interest. The technique adjusts for the variations in whole-brain uptake between animals and avoids many of the problems encountered in autoradiographic videodensitometry, against which technique it has been validated by Meibach et al. [24]. Values of RrCGlu were computed for each sample within each brain and the mean value obtained for each treatment to assess the effect of each treatment relative to that of the control group. RrCGlu values were then obtained by expressing each RrCGlu value as a percentage of the control treatment for each region of interest. The method with its advantages is discussed in more detail by Lipman et al. [25].

Drug Administration

Morphine (5 mg/kg) was administered by the intraperitoneal route and amphetamine (5 mg/kg) by the subcutaneous route 15 min before ^{14}C-2DG administration or the beginning of QEEG acquisition. Drug effects were, therefore, measured over 15–25 min following injection, a pretreatment interval shown in our preliminary studies to produce discriminable QEEG changes. These doses are within the same order of magnitude as Sasson et al. [7] have found to potentiate the rat escape threshold measure, although our amphetamine dose is somewhat larger (5 vs. 2 mg/kg).

Results

Behavioral Observations

Amphetamine produced typical hyperkinetic responses in rats so treated; with pronounced stereotypic rearing, sniffing, burrowing, licking movements and tooth chatter was apparent. The effect of morphine was to increase locomotor activity in the absence of stereotypy. No Straub sign was apparent in this strain of rat, although the tail was held in the axis of the body. The two drugs combined produced a behavioral syndrome which most closely resembled that of amphetamine, stereotypies being present. These behaviors commenced within 5 min after injection and persisted for the period of observation.

Effects of Drugs on RrCGlu

Despite their otherwise disparate pharmacological profiles, amphetamine and morphine were found to engender remarkably similar patterns of RrCGlu changes at the brain areas surveyed in this study, differing largely in degree (fig. 1). At no site that we surveyed did drug treatment change RrCGlu by more than 30% from control. At the occipitoparietal cortical sites corresponding to the QEEG electrode placements, RrCGlu was reduced similarly ($p > 0.05$) by both treatments. At eleven of the regions surveyed, amphetamine and morphine were found to evoke qualitatively different RrCGlu effects from each other: olfactory bulbs, superior colliculi, frontal cortex, cerebellum, geniculate bodies, medulla, septal nuclei, hypothalamus, hippocampus, amygdala, and caudate nuclei. Amphetamine treatment failed to change RrCGlu at olfactory bulbs, amygdala, hypothalamus, frontal cortex, and caudate nuclei, at which sites morphine significantly ($p < 0.05$) depressed it. At geniculate bodies, septal nuclei, and periaqueductal gray, where RrCGlu was similarly unchanged by amphetamine treatment, morphine enhanced it. At the superior colliculi morphine depressed RrCGlu, whereas amphetamine elevated it. At cerebellum and hippocampus, where amphetamine decreased RrCGlu ($p < 0.05$), morphine evoked only a small and highly variable decrease ($p > 0.05$) which was significant within the sensitivity of the method. At the medulla, amphetamine was found to increase RrCGlu, whereas morphine engendered no change ($p > 0.05$).

Effects of Morphine, Amphetamine, and Their Combination on QEEG

Separate Effects of Morphine and Amphetamine. The descriptive summary statistics of the effects of drug treatments are given in table 1 which illustrates the *relative* mean power (mV^2) measured from the QEEG power spectrum, averaged between left and right channels, from each rat of each group, expressed as a percentage of the control power which is also shown. It can be seen that both amphetamine and morphine evoked prominent and qualitatively similar increases in power in the frontal cortex. All frequency bands were affected, with the greater increases in power due to amphetamine occurring in the theta (3–7 Hz) and alpha (7–13 Hz) bands. In

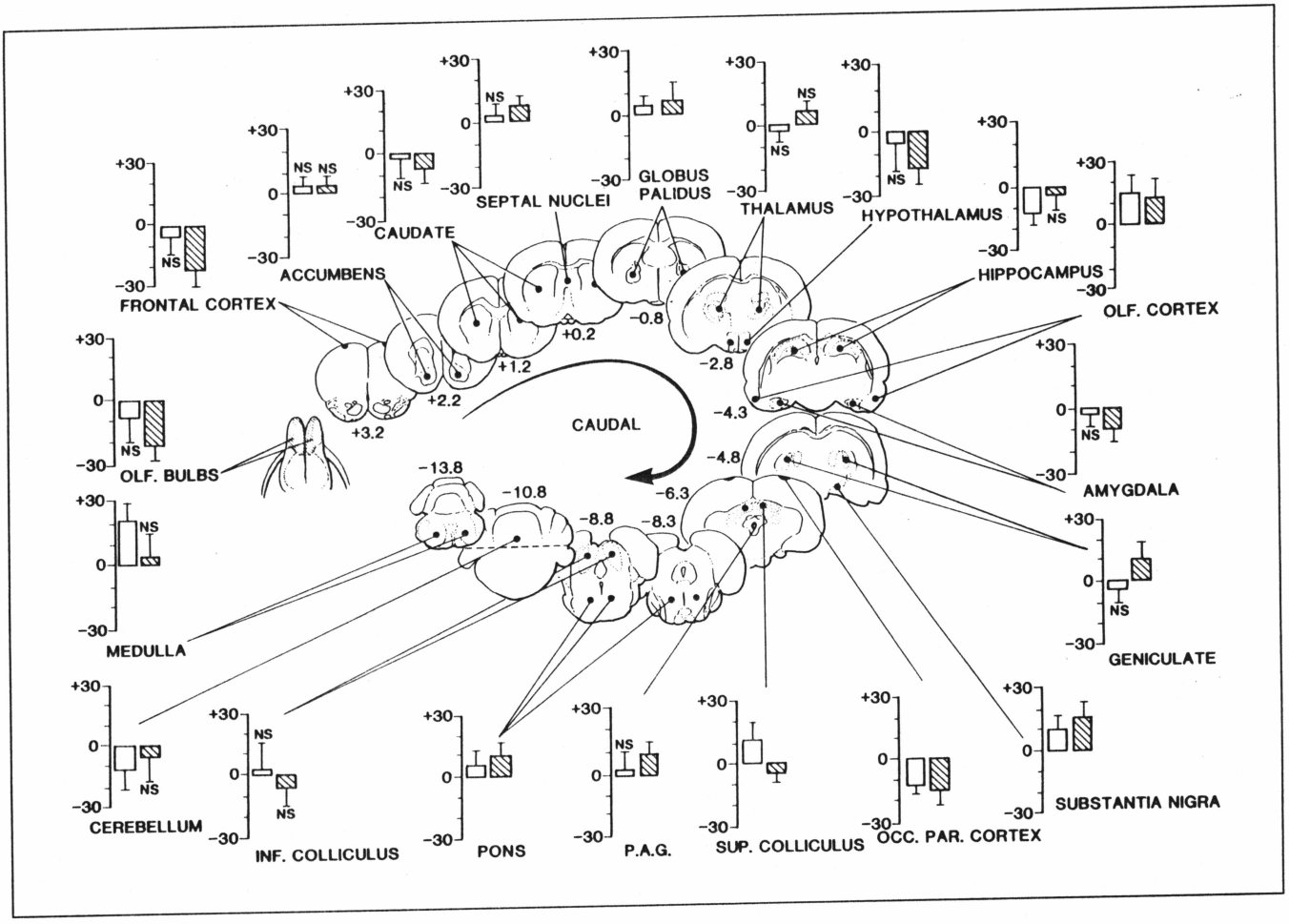

Fig. 1. Survey of RrCGlu (% of control) in brains of amphetamine-treated (open columns) and morphine-treated (hatched columns) animals. $p < 0.05$, except where indicated. PAG = periaqueductal gray.

Table 1. Group averages of the bilateral mean power (mV^2) expressed as a percentage of the control measurement (n = 13) measured in amphetamine-treated (n = 5) and morphine-treated (n = 13) animals and in those receiving the combined treatment (n = 8)

Amphetamine	Morphine	Amphetamine plus morphine	Frequency band	Mean control power, mV^2
Frontal cortex				
40.4	214	-17.9	delta	0.0517
327.0	351.2	64.1	theta	0.0188
570.2	260.4	49.7	alpha	0.1767
14.2	294.0	-40.0	beta	0.0577
Occipitoparietal cortex				
5.0	66.3	44.1	delta	0.1835
28.6	28.3	9.0	theta	0.1252
576.2	-42.0	45.4	alpha	0.0993
70.8	-16.1	-49.3	beta	0.0274

contrast, morphine greatly increased frontal delta (1–3 Hz) power and elevated beta (13–20 Hz) power in addition. Amphetamine could, therefore, be described as producing a relative shift in the background rhythm power to the theta and alpha bands, whilst the effect of morphine was reflected at all frequencies.

Smaller changes (increases) in power were measured at the occipitoparietal cortex: amphetamine prominently increased alpha power (576% greater than control), with a 701% increase in beta power. Morphine, on the other hand, caused relatively mild elevation of power within delta and theta bands (66 and 28%, respectively), with *reduced* power in alpha and beta bands. The two drug effects were thus discriminable at the occipitoparietal cortex, since amphetamine produced a relative shift toward increased power in the higher frequency bands, in contrast to the effect of morphine which produced a relative slowing of the occipitoparietal cortical rhythm.

Table 2. Standardized coefficients (by pooled within-group variances) of the variables of the two discriminant functions best separating the unique identities of the QEEG characteristics attributable to morphine-treated, amphetamine-treated, and control states

Electrode channel	Frequency band	Discriminant function 1 (x)	Discriminant function 2 (y)
LF	delta	−1.53255	−0.63482
LF	theta	−1.09348	1.97742
LF	alpha	2.01956	−0.30731
LOP	delta	−1.42587	0.26397
LOP	alpha	0.04919	0.26766
LOP	beta	1.00253	−0.93580
RF	delta	0.78089	0.17892
RF	theta	0.13598	−0.24036
RF	alpha	−0.54600	2.08275
RF	beta	−0.37715	−2.24851
ROP	delta	0.15192	−1.22748
ROP	theta	−0.19935	−0.40086
ROP	alpha	1.26346	−0.61806
ROP	beta	−0.97192	1.17613

LF = Left frontal; LOP = left occipitoparietal; RF = right frontal; ROP = right occipitoparietal.

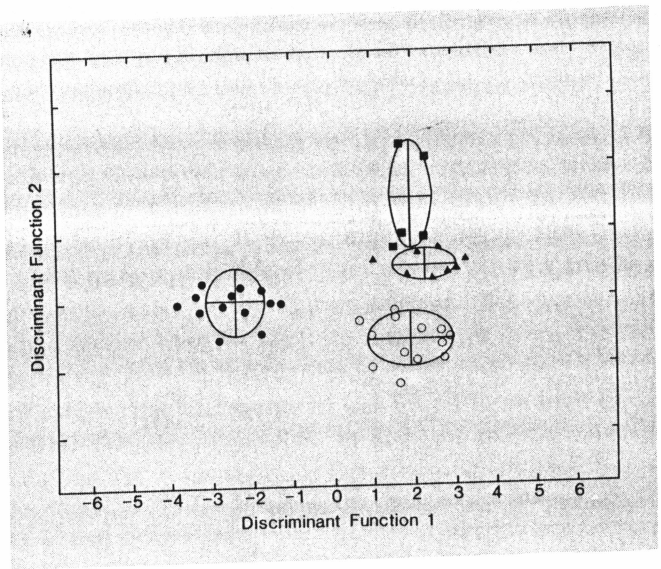

Fig. 2. Discriminant function (mean ± SD) graph illustrating the unique QEEG characteristics of the states recorded from animals treated with morphine (●), amphetamine (■), and the combination (▲) or in the control (○) state. Coefficients of the discriminant functions are defined in table 2.

Effect of Coadministration. The action of the two drugs in combination did not obviously resemble that of either drug alone, producing an apparently unique pattern of anomalies in the QEEG (table 1). Thus, the frontal delta power was reduced by the combination, whereas amphetamine and morphine elevated it (to differing degrees), and the frontal theta power was marginally increased by the combination, whereas the individual drugs engendered marked increases in power in these bands. At the occipitoparietal cortex the combination evoked apparently similarly unique changes that did not clearly resemble the power distribution of the individual agents.

In order to examine the subtle similarities and differences between the QEEG states' relative regional power distributions, data of the *control, amphetamine,* and *morphine* groups were subjected to discriminant function analysis for heuristic determination of these similarities and differences engendered by the different states. The method is particularly well suited to uncover complex combinational and otherwise covert relationships.

In discriminant function analysis three states are describable as the simultaneous solution of two dimensions or canonical (discriminant) functions. The variables of these functions were, in the present case, the raw powers (mV^2) of the frequency bands of each electrode channel. Coefficients are calculated in stepwise fashion for each of the variables of the two canonical functions, and these coefficients or *weighting factors* describe the relative importance of each variable in describing the uniqueness of the individual drug states reflected in the QEEG. In discriminant function analysis statistically identical groups of data occupy coincident intersections of the two discriminant functions, and nonidentical data occupy different intersections. We found that this method readily separated the three drug states' QEEG patterns from each other. Table 2 shows the weighting factors for the variables which comprise the two discriminant functions which best separate the three states: *control, morphine,* and *amphetamine.* According to the algorithm employed, F statistics calculated for each of these variables corresponded to the $p < 0.01$ level. In order to measure the similarities and differences between these QEEG states and that engendered by the *morphine plus amphetamine* combination, these weighting factors were applied to the data of the combination treatment animals' QEEGs and these plotted on the discriminant function graph (fig. 2).

It can be seen that the QEEG characteristics of the three drug states are each uniquely identifiable and distinguishable from the control state when analyzed in this manner. The drug combination moreover appeared to

Table 3. Standardized coefficients (by pooled within-group variances) of the variables of the single discriminant function that best discriminates the QEEGs of morphine- and amphetamine-treated animals

Electrode channel	Frequency band	Normalized coefficient
LF	delta	−0.44103
LOP	beta	−2.69869
LOP	alpha	2.79544
RF	alpha	−1.00774
ROP	delta	6.49425
ROP	theta	−1.78673
ROP	alpha	−0.34411
ROP	beta	−5.49449

For explanation of abbreviations see table 2.

more closely resemble the amphetamine state than the morphine state.

To investigate this phenomenon further, a second discriminant function was derived between the QEEGs of 'morphine' and 'amphetamine' states. A single function discriminates two states, as two functions discriminate three states. The derived function, having the variable coefficients listed in table 3, correctly classified 100% of the QEEGs entered into its derivation. As with the data of table 1, F statistics calculated for each of the variables correspond to the $p < 0.01$ level. The function was used to compute the discriminant score of the QEEGs measured from 'amphetamine plus morphine'-treated animals. The location of the three drug treatment groups' scores along the discriminant function continuum is illustrated in figure 3.

Discussion

Regional Cerebral Glucose Uptake

Because variations of whole-brain uptake commonly occur between animals, and in order to localize cerebral metabolic effects due to the drug states, methods for direct counting of microdissected tissue were chosen rather than the more common autoradiographic techniques with their attendant quantitation problems [26]. Precedents for these methods for localization of cerebral metabolic responses to functional activity are known in such applications as olfactory stimulation [27], peripheral nerve stimulation or visual deprivation [28], and effects of lysine vasopressin and adrenocorticotropic hormone fragments [29], adrenocorticotropic hormone analogues, α-melanocyte-stimulating hormone, and corticosterone [26] and naloxone [30]. More recently, the neurotoxic effects of aluminum salts have been quantified by this technique [20] and the cerebral metabolic consequences of the encephalopathy of uremia [25].

Our findings with regard to the distribution of cerebral changes in RrCGlu attendant on amphetamine treatment are substantially in agreement – with certain exceptions – with the work of others who have measured glucose utilization rates by videodensitometric analysis of autoradiography. In partial concordance with the work of Weschler et al. [31], we found that amphetamine enhanced RrCGlu in certain components of the extrapyramidal motor pathway, including the substantia nigra (+14%), with lesser, minimal, change in the globus pallidus (+8%), and no change in the caudate nucleus (−1.5 ± 5%). In agreement with the work of Weschler et al. [31] and that of Orzi et al. [32], we found that amphetamine did not significantly change RrCGlu in the mesolimbic system, including its terminal fields in the nucleus accumbens. Our findings of minimal change in amygdala, septal nuclei, and ventral hypothalamus are likewise in agreement. In contrast to the foregoing, the present method detected increased RrCGlu in olfactory cortex with decreased RrCGlu at occipitoparietal cortex, with no change at frontal cortex, whereas the method of Weschler et al. [31] identified decreased utilization at olfactory cortex and increased utilization at frontal and occipitoparietal cortices.

The acute effect of morphine on cerebral glucose utilization has been less well studied than that of amphetamine. Geary and Wooten [33], using an autoradiographic technique to measure rCGlu following a single large (50 mg/kg) dose of morphine, found a small – nonsignificant – decrease in uptake in all brain areas examined 1 h after administration. In contrast, Kimes and London [34], who measured glucose uptake in the brains of rats that had been implanted with a single 75-mg pellet of morphine 5 h previously, found reduced uptake in 6 of 37 brain areas surveyed. These included the interanteromedial and the gelatinous nuclei of the thalamus, the dorsal and ventral tegmental areas, medial raphe, and the dorsal parabrachial nucleus. Both the method of morphinization (dose, route, pretreatment time) and the method of quantification (videodensitometry of autoradiographs vs. direct counting) would seem critical to the interpretation of these data. In the present case – comparison of the effects of morphine and amphetamine – pretreatment time and quantification method were iden-

tical. Our data are thus internally consistent as to treatment and measurement method between control and treatment groups. The drug was the only variable in these studies, so that it seems reasonable to state with certainty that our data reflect the *relative* effect of these two drugs on RrCGlu of the rat brain, within the accuracy of our survey method.

Levy et al. [35] report that the relative ^{14}C-2DG uptake did not increase in the periaqueductal gray, a primary opioid-responsive region, following 5 mg/kg morphine in the rat. Their videodensitometric method of calculation, however, expressed periaqueductal gray uptake as a percentage of cerebellar uptake. Since our own data indicate a slight relative reduction in cerebellar uptake, which would have been undetected by Levy's technique, it is possible that these authors overlooked this effect. Our data confirm the finding by Levy et al. [35] of an increased uptake at the substantia nigra induced by morphine (fig. 1).

Quantitative Electroencephalography

The use of QEEG discriminant function analysis in a rodent model is a relatively novel application of this technique which has found greatest utility in the clinic. So powerful is this statistical method that it has spawned a novel scientific discipline which has been termed 'pharmacoelectroencephalography' [36]. Its principles were originally formulated as two hypotheses by Fink [37]: (1) EEG changes are directly related to the biochemical changes each compound induces in the brain, and (2) the behavioral effects are directly related to the biochemical effects.

The method has been used to identify an index (the theta:alpha ratio) which is diagnostic of the uremic encephalopathic state in the rodent and in man alike [25]. It has been used to compare the anxiolytic profile to that of antidepressant and neuroleptic drugs [38] and to evaluate structure-activity relations in novel hypnotic agents [39]. It has more recently found application in dissociating opioid from nonopioid effects of cyclazocine [40]. Most notably, the controversial idea that combined measures of cortical and subcortical spectral power measures may form a 'fingerprint' unequivocally describing the neuropharmacological class has been advanced by Dimpfel et al. [41, 42].

Separate Effects of Morphine and Amphetamine

Our finding that the QEEG state induced by amphetamine is characterized by increased power predominantly in alpha and theta bands (table 1) is consistent with the reported effect of this drug on humans. Such changes have been shown to correlate with alertness, concentration, extroversion, and mood [22]. Our finding of increased spectral power in the 0- to 20-Hz range arising from morphine treatment is likewise consistent with the data of Calligaro et al. [40] who found an average increase of 391 ± 10% commencing 5 min after a 10-mg/kg intravenous injection (cf. table 1). As regards the differences in the distribution of spectral power which characterize the two separate drug states, table 3 is instructive. As described earlier, the statistical significance of each variable assignment was found to be high ($p < 0.01$). The size (regardless of sign) of the normalized coefficients indicates their 'relative importance'. Right occipitoparietal delta power (1–3 Hz) contributes most to the state definition, followed by right occipitoparietal beta (14–20 Hz) and left occipitoparietal alpha and beta power. These data are in agreement with the observations on the characteristic effects of amphetamine reported by Matejcek [43].

Our data do not agree with those of Dimpfel et al. [41, 42]. Their studies, which do not employ parallel control groups and in which QEEG data are collected by radiotelemetry, reveal that frontal cortical QEEG power is depressed in the rat by both morphine (0.5 mg/kg) and amphetamine (2 mg/kg). Like ourselves, these authors assessed only one dose of each agent. Unlike ourselves, they used atypically low doses of morphine for this species, and their recordings were bipolar. Although their method of spectral analysis was identical to our own, they employed a 'logarithm of percent' transformation to smooth their data. Given these technical, methodological, and dose considerations, it is notable that the data of Dimpfel et al. [41, 42] and our own are each internally consistent (both drugs change frontal cortical spectral power in the same direction), yet qualitatively different from each other. Given the internal veracity of our own data as revealed by F statistics, leading to the discriminant function's ability to correctly classify 100% of each case, this discrepancy between the data of Dimpfel et al. [41, 42] and our own throws into question the 'fingerprint' concept, unless the method is explicitly specified.

Combined Effects of Morphine and Amphetamine

Superficial examination of the percent change in spectral QEEG power that results from coadministration of these two drugs (see table 1) might lead to the conclusion that the QEEG effects antagonize each other, leading to a metastate that is little changed from the control condition. Examination of the results shown in table 3

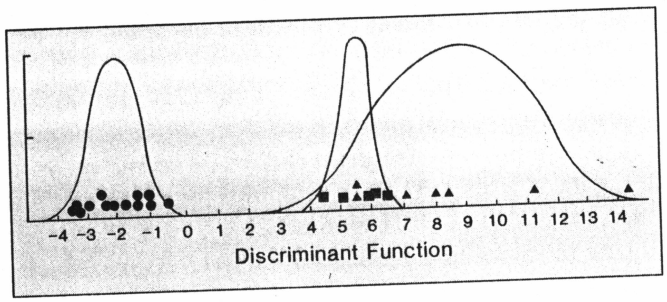

Fig. 3. Discriminant function plot of the discriminant scores derived from QEEGs of the morphine (●) and amphetamine (■) group animals. Scores derived using this function were computed for the QEEGs of the combination treatment (▲) and plotted on this same axis.

and in figure 3 reveals that this conclusion is simplistic. The *relative* effects between spectral frequency bands at each electrode more closely resemble a metastate that is amphetamine-like, yet is more extreme than amphetamine. That is, when the QEEG variables derived from animals treated with the combination are applied to the discriminant function separating morphine from amphetamine (describing the difference between morphine and amphetamine), the combination-treated group is described by a centroid further from morphine than is amphetamine. We conclude, therefore, that the combination treatment produces a QEEG metastate with few morphine characteristics.

Relations between RrCGlu and QEEG

Our finding that increased QEEG power due to either drug treatment was not correlated with increased cortical RrCGlu, but rather with decreased uptake, confirms earlier studies by ourselves and others that the energetic requirements of increased QEEG power are neither simple nor positive. In the present study, frontal cortical RrCGlu is depressed by morphine but not by amphetamine, yet both drug-induced states are associated with increased QEEG frontal power. We have previously shown that aluminum neurointoxication in the rat is associated with QEEG slowing with no change in cortical RrCGlu [20], and the same relationship is found in uremic encephalopathy [25]. As with the present findings, significant changes in subcortical RrCGlu correlated better with cortical QEEG variations. Identification of a causal relationship between these two variables (if, indeed, any exists) is hampered in the present case by the incompleteness of our survey. In the case of QEEG changes induced by uremic encephalopathy, slowing is associated with depressed RrCGlu in the hippocampus which in the present study was depressed in the face of increased QEEG power. From this inference we exclude a simple causal role for hippocampal glucose utilization alone in cortical QEEG power-frequency regulation. These general conclusions have been reached by others. Thus it has been observed by Young et al. [44] that sufentanil (an opiate) engenders EEG activation with decreased cortical glucose utilization. Sakabe et al. [45] find correlated decreases between cortical glucose uptake and EEG power in the case of pentobarbitone anesthesia, but not in that due to nitrous oxide.

Conclusions

Morphine and amphetamine engender qualitatively similar changes in RrCGlu in most brain regions surveyed, except at olfactory bulbs, frontal cortex, cerebellum, and lateral geniculate bodies. At those sites where the two drugs produced qualitatively similar effects, the effect of amphetamine was quantitatively greater than that of morphine at the doses used in this study. The effect of these two drugs on the QEEG was greatly different: both drugs increased frontal theta and alpha power, amphetamine to a greater extent than morphine. At the occipitoparietal cortex theta power was increased similarly by both drugs, yet amphetamine greatly increased alpha and beta power, whereas morphine reduced it. Discriminant function analysis of QEEG profiles revealed that the two drugs influenced the QEEG in different and discriminable ways, for each of which a characteristic pattern could be derived. When the two drugs were coadministered, the resultant QEEG profile was unique, yet bore closer resemblance to that of amphetamine than morphine. This finding has important implications for our understanding of the 'speedball' effect. Clearly the electrophysiological consequences of coadministration closely resemble, yet are discriminably different from, that of the amphetamine state. Insofar as cortical electrophysiology reflects cortical function, these data suggest a biological basis for the clinically observed phenomenon that opiate coadministration with sympathomimetics (including cocaine and the amphetamines) rapidly leads to the user's addiction escaping from control [46, 47].

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