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Introduction to Symposium on Endorphins and Behavioural Processes; Review of Literature on Endorphins and Exercise

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STEINBERG, H. AND E. A. SYKES. *Introduction to symposium on endorphins and behavioural processes; Review of literature on endorphins and exercise.* PHARMACOL BIOCHEM BEHAV **23**(5) 857–862, 1985.—The first symposium on endorphins and behavioural processes in Britain was held by the British Psychological Society in March 1985. Against a background of the explosive history of the discovery of endogenous opioids, problems of terminology, and basic mechanisms and concepts, five papers reflect the main fields in which outstanding progress has been made: analgesia, feeding, reward mechanisms, social behaviour and aggression, and addiction. A review of the literature on endorphins and exercise stresses both the value and limitations of trying to unravel a fashionable subject. Endorphin research is multi-disciplinary and highly complex, with tricky technical and conceptual problems and inevitable lack of consensus. Investigators should be more aware of the crucial role that outcomes of behaviour experiments play in the attribution of function to opioid systems.

Endorphins Behaviour Exercise

BACKGROUND

The papers which follow constitute the first symposium on endorphins and behaviour to be held under the auspices of the British Psychological Society, on 31 March 1985 in Swansea. The initiative for it came from a small group of active British psychologists who had been quick to follow up important new developments and opportunities in opiate research, and whose work has become part of the international corpus.

The idea that the brain can 'manufacture its own opiates' continues to be regarded by some as strange and miraculous, though to those who have been working at the interface of brain and behaviour it may, especially with hindsight, appear not only plausible but obvious. The central daunting problem was, and is, to identify and characterise substances, to analyse their origins, actions and interactions, and so to reach an understanding of functions and of underlying mechanisms. What gave this endeavor enormous impetus in the 1970's was not only serendipity and a 'ripe' body of knowledge, but also the refinement of techniques such as radioimmunoassay, which made it possible to detect the sometimes vanishingly minute amounts of endogenous substances involved.

HISTORY

The discovery of endorphins has indeed a long past (e.g., [36]) but a short history, which has been much told. For interesting outline versions, tracing the strands of contributions from different research workers, see [20, 27, 28, 35, 56, 58, 64].

It will soon be 10 years since one of the main landmarks appeared in Britain. On 18 December 1975, Hughes, Smith, Kosterlitz *et al.* reported in *Nature* [29]—a much thumbed and now disintegrated article in at least one university library—the structure of two pentapeptides, met-enkephalin and leu-enkephalin, isolated from pig brains. These peptides had potent opiate agonist activity, and together composed the previously discovered substance 'enkephalin' (from Greek: *enkephalos*: 'what is within the head;' brain). This had been shown to inhibit the contraction of isolated smooth muscle, as opiates do; the inhibition was blocked by opiate antagonists.

A frenetic growth of research on endogenous opioid peptides, as well as on the existing opiate drugs, occurred, which had enormous fundamental and practical implications, and which continues today. The amount and scope of the resulting literature can be bewildering—for example, Olsen *et al.*'s 'non-exhaustive' review of publications in 1981 contains 585 references [45]. A short commentary such as this, therefore, is perhaps best regarded as a small blurred still from a fast-moving film.

From a practical point of view, the main aim probably remains to discover powerful pain-relieving substances which are free of the hazards of existing opiate analgesics, such as depressed respiration and addiction liability. But, as is also implied by the papers in this symposium, the possible

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clinical ramifications go much further, into psychiatry, drug dependence, endocrinology, immunology and aspects of cardiovascular regulation, including shock and 'stress' [11,66].

The pharmacology, physiology and biochemistry of both exogenous and endogenous opioid substances are turning out to be increasingly complex (e.g., [3, 43, 47, 51, 52]) and some of this is reflected in terminology.

TERMINOLOGY

'Opiate' strictly refers to the products derived from the juice of the opium poppy, but has been traditionally used for morphine and structurally similar substances such as codeine and semi-synthetic congeners of morphine. When wholly synthetic substances with opiate-like actions became available, 'opioid' ('opium-like') began to be applied to all drugs, natural or synthetic, with actions of this kind, though in practice 'opiate' and 'opioid' were often used interchangeably. Later, following the discovery of endogenous substances with opiate-like actions, it was suggested [28] that 'opioid' should refer to any directly acting compound, all or some of whose effects are stereospecifically antagonised by naloxone, a relatively 'pure' competitive antagonist drug; 'opiate' could then be reserved for the exogenous sub-group of morphine-like alkaloids. A *Lancet* leader [37] has proposed that 'opiate' should be avoided altogether in favour of the all-embracing 'opioid,' and praises the 1980 edition of Goodman and Gilman's authoritative textbook [30] for doing so; Goodman and Gilman, however, reserve 'opioid' for exogenous drugs and use 'opioid-like' for endogenous opioid peptides ([30] chp 22), which at first sight appears tautologous (the forthcoming seventh edition of Goodman and Gilman, with its revised section on opioids, is awaited with interest.) It is not surprising that interchangeability and inconsistency continue. If two terms are still needed, then (endogenous) 'opioid peptide' and (exogenous) 'opiate alkaloid' are perhaps most congenial, with 'opioids' as the umbrella name for both. 'Narcotic analgesic,' it has been further suggested [28], should be reserved for compounds producing naloxone reversible-analgesia, though some (e.g., [30]) consider the word 'narcotic' ('benumbed') confusing and obsolete.

'Endorphin' ('endogenous morphine') has also had a somewhat mixed history. It was originally proposed by Simon [56] as a class name for the proliferating newly discovered endogenous peptides, but was then used in a more specialised way for particular sequences within β-lipotropin—e.g., C-terminal fragment became known as β-endorphin—and 'opioid peptides' has therefore been recommended as the generic name [28]. However, 'endorphins' has etymological attractions as a generic term and is certainly euphonious, and so it is likely to continue to be used in this sense—hence the title of this Symposium—as well as in the restricted sense of a sub-group or 'family.'

At least three 'families' of endogenous opioid peptides [52] now seem to be generally distinguished: *enkephalins* (the original two [28] to which others have since been added), *endorphins* (larger and more stable than enkephalins); and a more recently discovered third group *dynorphins* ('powerful morphines'). These sub-groups have structural similarities but differ in their detailed distribution in the nervous system, their precursors and in receptor activity, that is, their interaction with specific binding sites on/in cells. Multiple forms of opiate receptor are now recognised, elaborating upon those originally defined as mu (morphine), kappa (ketocyclazocine) and sigma (SKF-10047). Attempts to pair opioid peptides with receptor-types have led to significant correlations, though whether any of these is unique is uncertain [3].

At the *in vivo* level, the new discoveries have led to further complications of procedure and interpretation. Thus, discrepancies in response, attributable to different routes of administration, dose sizes, unusually shaped dose response curves, chemical instability and/or biological rhythms, though not new in principle, can be extreme in practice (e.g., [32]). But these are heavily outweighed by the critical and useful tools, concepts and constructs for behavioural scientists [3, 5, 52] that have already emerged from research on opioid systems. This is well illustrated by the papers in this symposium.

SYMPOSIUM PAPERS

Thus, Colin Hendrie argues strongly for the role of adrenocorticotrophic hormone (ACTH) as an endogenous excitatory 'contra opioid' agonist. This could also help to explain how naloxone, an exogenous antagonist, attenuates withdrawal symptoms in opioid dependent animals: it might restore the normal balance between opioid- and ACTH-mediated influences, which had been upset by withdrawal.

David Benton deals with aggression, and the impact which novel opioid compounds are making on its analysis. From interactions between experimentally anosmic (and hence submissive) mice and intact ones, and using two compounds thought to act at different receptor sites, he is able to suggest a possible correspondence between increased submission and a kappa mechanism, and decreased submission and a mu mechanism.

Ian Stolerman neatly places opioids in the general context of the stimulus effects of drugs: opioid agonists have consistently rewarding effects on behaviour, though aversive effects of antagonists are far less robust. Because of inconsistencies and insufficient information, especially on the opioid peptides, conclusions about detailed involvements of enkephalins in reward-aversion processes must, however, be cautious.

John Rodgers and Jill Randall report further work on 'social conflict' analgesia in intruder mice which follows attack from aggressive residents. Their compact but model investigation shows how opioid antagonists and cross-tolerance with morphine can be used to establish opioid involvement in an originally non-opioid, i.e., behaviourally induced, form of analgesia.

Finally, Steven Cooper, Anne Jackson and Timothy Kirkham conclude, from an impressive review of the literature on food intake, that different endorphin mechanisms could now be said to have specific relations with different aspects of the feeding process in rats, such as satiety, preference for highly palatable foods and hyperphagia.

Between them, these papers discuss or touch on most forms of behaviour which are being prominently studied in relation to opioids: pain, feeding, aggression and social behaviour, reward systems and addiction.

What follows is a brief review of another subject that has recently begun to orbit, partly because of widespread popular interest: physical exercise.

ENDORPHINS AND EXERCISE

Although the link between exercise and endorphins has

now been reified through the media ('exercise releases endorphins which do you good'), it is neither straightforward nor conclusive.

It also depends on several analogies between effects of exercise and those of opioids: first, reports that exercise can produce a 'high,' that is, emotional states of euphoria and enthusiasm similar to states described after ingestion of opioids; secondly, findings that tolerance of pain increases after exercise, as after administration of opioids; and thirdly, the more general idea that exercise can, in many respects, behave like an addiction, similar to opioid addiction.

These analogies are supported by a stimulating (e.g., [46,54]), though till recently largely descriptive, anecdotal and scattered literature. Superficially, exercise research seems attractively straightforward, but it is beset by methodological and practical problems.

Different kinds of exercise, physical fitness and changes therein are hard to define, to measure and to compare [14,44]. Therefore it is difficult to establish relations between them and other factors, such as the psychological; the valid measurement of these of course has its own problems. In interpreting results it is moreover necessary to distinguish between the effects of exercise *per se*, and those of other components which might themselves be beneficial; thus, engaging systematically and collectively in any organised activity might have similar benefits. Interestingly, there was already evidence in the 'pre-endorphin' early 1970's that, in laboratory animals, behavioural responses to exogenous opioids are influenced by their social history [1, 2, 33, 34, 49, 62]. For such reasons, scientifically valid confirmation of the analogies is still relatively sparse. This is particularly true also of direct evidence for opioid involvement, such as changes in plasma endorphin levels with exercise, or effects of opioid antagonists.

MOOD

It is now regarded as established that exercise can induce positive moods in normal subjects and have antidepressant effects in depressed patients [16, 21, 39, 42, 46, 48, 59], though the absence of mood changes with exercise has also been reported [23, 26, 44]. On this basis exercise programmes have been recommended for the treatment of depressive illness [17,53].

This need not necessarily imply involvement with opioid mechanisms. Temporary positive moods can be induced by a variety of substances other than opiates and by environmental conditions [63], and results of trying to use endorphins clinically as antidepressants have been inconclusive [8]; self-medication with opiates—and hence addiction—does, however, often seem to start as an attempt to alleviate depression.

Where endeavours have been made to link exercise-induced mood changes more directly with endorphins, the results have also been equivocal. For example, Markoff *et al.* [42] failed to find any effect on running-induced positive mood changes with 0.8 mg naloxone given subcutaneously, though Janal *et al.* [31], using the same dose, twice, and by intravenous injection, found that it attenuated self reports of 'joy' and euphoria; it also reversed post-run ischaemic hypoalgesia. The dose and method of administering the antagonist may have been important here (see also [25,44]), which on general pharmacological grounds would be unsurprising.

Naloxone on its own seems to induce mildly dysphoric mood changes in man; it is also increasingly being found to produce a variety of inconsistent, mixed and marginal effects, both in isolated tissues and on behaviour (cf. [23]). For example, even high doses have not usually been found to intensify experimental pain in man. Although naloxone will probably remain a powerful tool in opioid research, caution is needed in judging opioid system involvement on the basis of naloxone antagonism or its absence alone [20].

In a recent review Morgan [44] concludes that the much-vaunted phenomenon of 'runners' high,' despite copious documentation (e.g., [41,46]), is too vague to be regarded as validly established. There is little doubt that running and other exercise can lead to powerful changes in emotional states, but exercise-induced euphoria may or may not be analogous to euphoria produced by opiates, other drugs or non-drug means [63]. Introspective descriptions seem insufficient, and it is both possible and necessary to use acceptable scientific methods to manipulate altered states of consciousness, whether induced by drugs, exercise or otherwise (cf. [60,65]).

Colt *et al.* [12] have argued that plasma β-endorphin rises after exercise are much smaller than those induced in psychiatric patients treated with large doses of β-endorphin intravenously, and that therefore mood changes such as 'runners' high' are unlikely to be attributable to the small post-exercise rises.

ANALGESIA

It has long been known that pain perception can decrease during periods of stress or great emotional excitement as well as under the influence of administered opioid drugs. Experimental pain sensitivity as a result of exercise has been studied in long-distance runners [31] with, on the whole, positive results: post-run pain threshholds with two of the tests for inducing pain increased; the plasma levels of β-endorphin, ACTH, prolactin and growth hormone increased, and naloxone reversal occurred with one of the pain tests (ischaemic pain). As described under 'Mood', post-run mood assessments were favourable, but less so after naloxone. Naloxone blocking of jogging-induced analgesia has also been reported by Haier *et al.* after using 10 mg naloxone, but not after 2 mg IV, which actually enhanced analgesia [25].

In an interesting animal study by Shyu *et al.* [55], rats were trained to run spontaneously (rather than 'forced' to exercise as in most other investigations, see [15]) for 3 weeks, by the end of which some averaged as much as the equivalent of 7 km per night. Squeak thresholds to electrical stimulation were raised after a night's exercise, and the size of the increase was correlated with the distance run. Naloxone injection reduced squeak thresholds almost to control levels.

In recent years stress-induced analgesia has attracted intense research activity, especially with laboratory animals, though the exact involvement of opioid mechanisms remains understandably controversial [3,40]. Exercise may perhaps be viewed as an acceptably convenient stressor for research purposes, including in man, and exercise/analgesia research therefore has theoretical as well as practical potential.

ADDICTION

A substance or situation may be regarded as 'addictive' if: (1) it produces, not necessarily immediately, pleasurable emotions such as the 'high' already discussed, which lead to

continued administration; (2) there is tolerance in the sense that more of the substance or situation is needed to maintain this pleasurable effect; and (3) there are withdrawal signs if administration is discontinued, which can only be relieved by reinstating the original substance or situation, or by suitable substitutes. Cross-tolerance with related substances or situations and responsiveness to appropriate antagonists would add further weight. Although exercise, and running in particular, has been said to satisfy the three major criteria [41, 46, 53, 59], systematic evidence is predictably sparse and inconclusive, with inherent problems of suggestion, expectation, motivation and so forth.

For example, deprivation from exercise is particularly hard to investigate experimentally, since 'addicts' can rarely be induced to give up exercise voluntarily; therefore one may have to rely on athletic injuries, with possible other confounding effects. In a useful, though 'pre-endorphin' study of sleep [4], subjects who were willing to forego regular exercise for one month were eventually recruited by offers of higher than usual payment. However, they turned out to be a selected group, rather less committed to running than those who would not volunteer. Nonetheless, deprivation seemed to produce 'withdrawal symptoms,' such as changes in sleep patterns consistent with increased anxiety, as well as subjective effects, including greater sexual tension and more need for the company of others.

Promising animal experiments on aspects of exercise addiction are discussed in [15,44].

The idea of an 'addictive personality type' has received relatively little support from research into dependence on opioids or other drugs, but exercise investigators have continued to look with interest at personality characteristics, especially of runners.

From a review of the literature—some 40 studies—Sachs [53] has concluded that the results are equivocal. Despite some plausible pointers, e.g., runners may tend to be introverted, stable, low in anxiety, self-sufficient, imaginative and high on self-esteem, the evidence is too problematic to justify generalisations. Pargman and Baker [46] have come to a more positive opinion in their review, and suggest that the psychological profile of addicts of any type—narcotic or exercise—may have similarities.

ENDORPHINS IN PLASMA

Results of measurements of opioids in blood plasma before, during and after exercise, especially running, began to be published around 1980 [50]. In virtually all cases, β-endorphin levels, mostly in trained runners, increased significantly concomitant with exercise, as did levels of hormones such as ACTH, prolactin and growth hormone where measured [7, 12, 18, 31]. Results of naloxone administration, in a number of cognate studies reviewed in [23], have however been judged inconclusive (see also [9]).

Howlett *et al.* [26] found changes not only in β-endorphin in female subjects' responses to treadmill exercise but also in met-enkephalin, which in a previous study with males [23] had been unchanged. Significant release of β-endorphin occurred before, during and after an intensive programme of exercise training; met-enkephalin increased dramatically in untrained subjects, but this was almost abolished by training (cf. [6]). It was concluded that opioid peptides play a part in adaptive changes to exercise training and possibly in menstrual disturbances of women athletes (cf. [10, 19, 38]).

From a review of the β-endorphin changes in male subjects, Farrell [15] found that the size of the increases varies greatly from slight to 5-fold, and that they correlate poorly with intensity of exercise. This may have been due in part to methodological differences, which made comparisons between studies difficult. Recently [13] individual differences in β-endorphin increases in response to exercise have been demonstrated to depend markedly on the exact post-exercise times at which blood samples are taken. Moreover, procedures such as cannulating exercising subjects in order to obtain blood samples could create further individual differences.

The biological significance of rises in plasma levels of endogenous opioids with exercise is unclear. As various authors point out, inferences about central nervous system levels or functions cannot be drawn from peripheral levels alone. In addition, exercise is accompanied by numerous other physiological and biochemical changes; many of these, especially the cardiovascular, are linked with catecholamine activity. It seems possible that endogenous opioids dampen the release of catecholamines induced by any form of severe stress, but the establishing of the precise role of endorphins in exercise awaits further work, particularly upon the receptors themselves.

CONCLUSION

What in summary can be conluded from the diverse evidence (for further reviews, see [22, 24, 50, 57]) about exercise and the involvement of endorphins?

Given the inherent difficulties, complexities and *caveats*, the following are suggested:

(1) Exercise has reward value, and its effects do in many respects appear to mimic those of acute or chronic opioid administration; exercise might in some circumstances be used as a non-drug substitute.

(2) Plasma levels of β-endorphin have universally been reported to increase with exercise, especially running, and this may turn out to be true of other endogenous opioids as well. The precise biological importance of these changes has yet to be elucidated.

(3) Exercise should be viewed in the broader context of physical and psychological stress. It is only one of a number of stressors which may interact with opioid systems, possibly, for example, to inhibit extreme reactions to stress and so improving 'coping.' It remains to be discovered how far similar mechanisms are involved in each.

More generally, exercise/endorphin research strikingly illustrates once again the value and mutual interdependence of behaviour, brain and biochemistry. By a process of 'successive approximation' [61], problems and technical and conceptual tools from different disciplines can be progressively refined and their validity checked against each other. Since, in most cases and whether we like it or not, behaviour is the final arbiter for attributing function, the stepwise and expert approaches of the five papers in this symposium are particularly commended.

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