



REVIEW

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The effects of Beta-Endorphin: state change modification

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Abstract

Beta-endorphin (β -END) is an opioid neuropeptide which has an important role in the development of hypotheses concerning the non-synaptic or paracrine communication of brain messages. This kind of communication between neurons has been designated volume transmission (VT) to differentiate it clearly from synaptic communication. VT occurs over short as well as long distances via the extracellular space in the brain, as well as via the cerebrospinal fluid (CSF) flowing through the ventricular spaces inside the brain and the arachnoid space surrounding the central nervous system (CNS). To understand how β -END can have specific behavioral effects, we use the notion behavioral state, inspired by the concept of machine state, coming from Turing (Proc London Math Soc, Series 2,42:230-265, 1937). In section 1.4 the sequential organization of male rat behavior is explained showing that an animal is not free to switch into another state at any given moment. Funneling-constraints restrict the number of possible behavioral transitions in specific phases while at other moments in the sequence the transition to other behavioral states is almost completely open. The effects of β -END on behaviors like food intake and sexual behavior, and the mechanisms involved in reward, meditation and pain control are discussed in detail. The effects on the sequential organization of behavior and on state transitions dominate the description of these effects.

Keywords: Beta-endorphin, Behavioral states, Behavioral sequences, Cerebrospinal fluid, Volume transmission, Feeding behavior, Sexual behavior, Pain, Reward, Meditation

Introduction

States

An organism, from a single cell to *Homo sapiens*, continuously responds to input from its environment with (if all is well) an adequate action. Such input-action pairs only partially describe the organism. Indeed, the same external stimuli may give rise to a different reaction. In that case we say that the organism is in a different (internal) *state*. In this way states are defined as action tendencies. The state of an organism may vary from moment to moment. Therefore we define the state of an organism (the notion also applies to mechanical systems with sensors and actuators) at a given moment t , as the way it acts when receiving certain stimuli at moment t . Thus a state is an idealized mathematical notion, that usually cannot be known in full, but that is nevertheless very useful: it can be approximated and can serve for

theoretical considerations. The notion of state is used in computer science [1] and also extensively in mathematical system theory. Prior to this, statistical mechanics described the state of a gas in a vat as elements of a space of dimension $6 \cdot 10^{23}$, where the 6 stands for the 3 position coordinates plus 3 velocity components of the 10^{23} (Avogadro's number) molecules in a given volume. Such complex states cannot be determined empirically nor theoretically, but serve to derive the well-established laws of thermodynamics.

Approximating states, sub-states

As approximation to a state in an organism, one can consider a vector of variables having a given value [2]. Indeed, in the ideal case of having all possible values, such a vector completely determines the behavior of the organism, depending on presented stimuli. A *sub-state* is a part of this vector of values, determining only partly the input-action relation. For the notion of state one may restrict oneself to relevant forms of input and action, depending on the context of the subject matter.

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These are sub-states relevant in a certain scientific context. For example, in studying a species one may restrict oneself to feeding or to sexual behavior. In such cases one speaks about *behavioral states*. For *Homo sapiens* another restriction is useful: it makes sense to focus on signals available to consciousness and to intended actions. Then one speaks about *mental states*.

The notion of state is a so-called higher-order mathematical notion. A state is not involved with just one input signal and one action signal, but with a whole class of input-action signals. Making restriction eases the fact that states are higher-order mechanisms and can be helpful to obtain experimental or theoretical results. The well-known human emotions (like anger, fear, desire, surprise, disgust) are all examples of mental sub-states of a more general mental state. They are sub-states because one can be angry and fight, or angry and submissive, hence indeed some parameters are lacking.

Phases: keeping some sub-states fixed

By the definition above, a state is momentary, occurring at a precise moment in time. A sequence of related (e.g. when a certain sub-state being fixed) states during an uninterrupted interval of time can be called a phase. An example is an animal in the state of being hungry. It is looking for food in order to eat. Usually the state of hunger remains, even if food is found and the animal is eating. In this phase of eating, the sub-state hunger is more or less fixed. It has to persist for obvious reasons: one bite of food is not enough. But the persistence of hunger is not exact; it (gradually) diminishes, for otherwise the animal would (in the condition of abundance of food) never stop eating. Another example of a phase with a constant sub-state is sleep. The mechanisms for sensorial input and muscular output are for a large part blocked. But during the phase of sleeping not all sub-states are the same: one can distinguish rapid-eye movement (REM) and non-REM sleep. In both examples phases may be divided into several sub-phases.

It should be emphasized that the notions of state, sub-state, phase, and sub-phase are all quite natural and familiar. Talking about the weather, the notion of (momentary) state corresponds to the familiar values indicating the temperature, air-pressure, direction and speed of the wind, humidity, etcetera, all at one given moment. The notion of phase that lasts for a certain time interval applies to what we usually call the weather. Indeed, a rain storm consists of an uninterrupted flow of states having in common that it is both raining and windy. Exactly how much rain is falling and whether there is also lightning (a sub-state at a given moment) may vary during the interval of the phase of the rainstorm. So there is place for sub-phases: "During the rainstorm the lightning lasted unusually long." We

see that the notion of (momentary) state is fundamental, while phase refers to a continuous time interval during which the momentary states are similar but not necessarily equal, for example by keeping some of the sub-states constant. The concept of phase is very different from that of state. There is a precise mathematical definition of what is a state. What is a phase depends on what one considers to be comparable. When exactly does a storm end? One could say: "If no longer there are gusts of wind with speed 150 km/hour." Here there is a place for choice (possibly very relevant for aeronautics). In the case of state at a given moment, there is no choice.

Change and maintenance of states

In an organism with a CNS, induction of a new sub-state in which a couple of parameters are to be changed, can be organized efficiently using action potentials and synaptic transmission. If, on the other hand, there is a need for maintenance of a sub-state, in the terminology above for a certain phase, there seem to be several natural possibilities for doing this. 1. Sustained neural activity, using synaptic transmission. 2. Local volume transmission (VT) to keep certain chemical parameters locally at the right level. 3. If parameters need to be changed globally into a certain direction, then volume transmission through the cerebrospinal fluid (CSF-VT) is an option (see Table 1). For animals with a developed CNS, we have argued that there is a mixed usage, in particular for neuropeptides like oxytocin and β -END [3-5]. It has been shown that the mechanisms work in parallel: a fast ephemeral axonal message transports the signal of a peptide to relevant areas; after that the slower but longer lasting volume transmission does its work. Via second messengers, the effects of VT may last much longer, up to months, years or even life-long [6-11]. This may be related to the question why there are so many neuropeptides and what is their relation to the variety of different behavioral states.

Numerous findings in the literature can be explained by simply assuming that neuroactive substances, released at specific points in the brain along the ventricular system, reach their distant target areas by 'going with the flow' of the CSF. This particular kind of long-distance-VT has been included in all discussions concerning VT [6,11-15] and in fact β -END was among the very first

Table 1 The effects of β -END in the CNS

β -END effects in the CNS	Short term	Long term
Local	Synaptic transmission	Volume transmission
Regional and global	Volume transmission	Volume transmission via CSF

In the present as well as in our preceding paper (Veening et al. [5]) a variety of CNS-effects have been described for β -END. The available evidence suggests that this neuropeptide exploits all kinds of messaging available in the CNS.

substances mentioned in relation to VT [9,11]. Meanwhile, the effects of substances released from particular parts of the brain into the CSF to target distant brain areas have been studied for a variety of substances such as vasopressin, corticotropin-releasing-factor, gonadotropin-releasing-hormone, melatonin and oxytocin [3,4,16-22]. Recently, we have reviewed the available evidence showing that β -END is another neuropeptide that can be released into the CSF to affect distant brain areas [5]. Most neurons producing β -END are located in the arcuate nucleus (ARH) of the basal hypothalamus, alongside the third ventricle, but an additional, smaller group has been observed in the caudal brainstem. The involved ARH-neurons produce a mixture of neuropeptides and are known as proopiomelanocortin- (POMC-) neurons (for further details, see [5]).

The present review discusses more specifically the potential of CSF-flow to influence a number of brain areas together, to induce behavioral (state-) changes. The behavioral data, provided below, show on the one hand that certain brain manipulations with β -END have a special effect on specific behavioral transitions, thereby effectively blocking transitions to another behavioral phase. On the other hand, β -END induces general behavioral effects, described by several authors as 'a state of well-being' (see below), which also clearly suggests that the effects of this neuropeptide are state-related. The present review focuses on such behavioral effects of β -END and in addition we discuss states and their selection and preservation on the basis of the Turing-model [23] inspired by Turing [1]. Actually it is a hybrid model that is also inspired by the neural nets introduced in Turing (1948), see [24,25] describing artificial neural nets, a connection already pointed out previously [8].

The sequential nature of behavioral states in human cognition

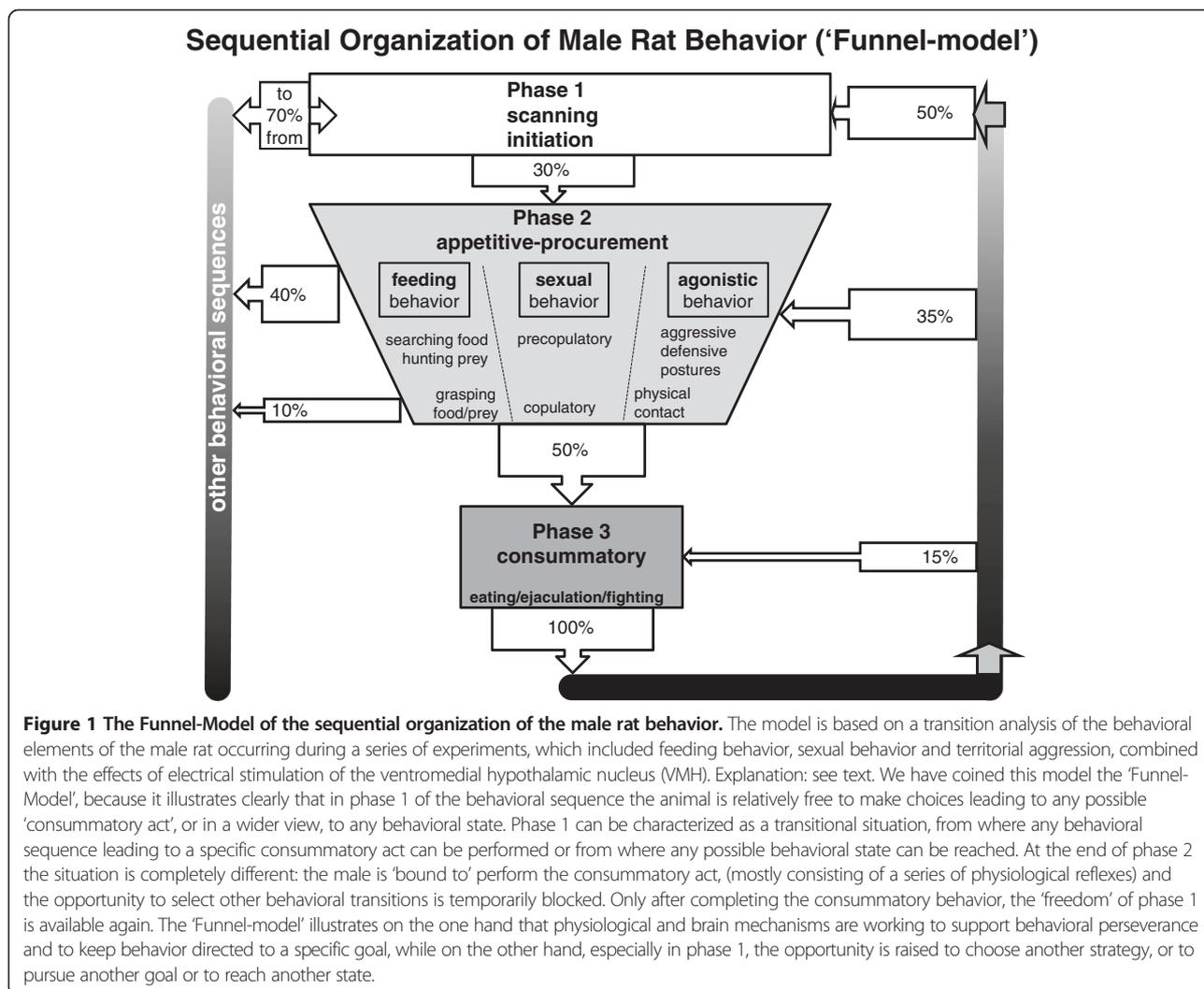
In Zylberberg *et al.* [26] and Barendregt & Raffone [23] human cognition has been independently described as a 'discrete hybrid Turing machine'. This means the following: 1. [Discreteness] actions proceed in a serial way (one after the other, like a fast ticking clock, not continuously); 2. [Turing machine] these actions do not only depend on the stimulus (a demonstrable drawback of behaviorism), but also on the state of the organism/machine; 3. [Hybrid machine] how a given stimulus and state produce an action is determined by a parallel neural net (unlike in the classical Turing machine, where these transitions are described by an explicit table). The model is quite simple: important events, state changes and actions, are occurring in a discrete serial fashion, depending on the previous state and the input. Among the possible actions, focusing attention is an important one. This is the full model description. The discreteness

of human cognition is supported by psychophysical evidence on visual illusions and periodicities in reaction time (for a review see [27], as well as by electroencephalographic evidence about discrete brain microstates, (see [28]). Paper [27] emphasizes different aspects than does [28]. For example the first paper beautifully answers the question of John von Neumann how it is possible that human cognition answers questions with high accuracy while there is biological noise. The answer by Zylberberg *et al.* [26] is convincing: "by discretization" (like a CD avoids the noise of an old-fashioned vinyl record). The second paper [28] emphasizes the use of states, and employs the notion of a universal Turing machine (programmable computer) in which states can be used as input. This enables modification of automatic behavior.

The sequential organization of animal behavior: a 'funnel model'

In a behavioral study of rats [29,30] the structure of feeding, sexual and agonistic behavior was analyzed by means of an extensive transition analysis of the successive behavioral elements. In some experimental situations, regular transitions were interrupted by electrical stimulation of the ventromedial hypothalamic nucleus of the freely moving rat. This approach showed not only the normal succession of behavioral elements in each of the behavioral sequences, but also the interruptive effects of the medial hypothalamic stimulation. These effects were strongly dependent on the moment of delivery during the behavioral sequence: during the 'scanning'- or initial phase the normally succeeding transitions towards the appetitive and consummator phases appeared to be completely blocked. When stimulation started during the succeeding, appetitive, phase, the experimental animal tried to 'switch back' to the initial phase, as long as possible. However, when the brain stimulation was delivered in the final phase, animals tried to 'complete the sequence' before returning into the initial phase. These findings together are the basis for the 'Funnel Model', [29-31] describing the organization of behavior of the male rat, as depicted in Figure 1.

In phase 1 the resident animal is just scanning the environment, with some sniffing and locomotion, and for the observer it is not yet clear in which direction behavior will develop. If, however, palatable food or an estrous female or a male intruder is introduced into the resident's cage, its behavior rapidly changes into the appetitive/procurement phase, with characteristic and species-specific and goal-directed behavioral elements to obtain the food/prey, to perform (pre)copulatory activities or to approach and threaten the male intruder. In the final consummatory/executive phase, food consumption, or ejaculation or biting and fighting occur, until the intruder shows submission or leaves the field.



In this final phase, the behavior contains many 'reflexes', organized at the level of the brainstem and spinal cord, like chewing and swallowing, ejaculation as controlled by the spinal ejaculation center [31-34] or an extremely fast series of biting and fighting movements. At the end of the consummatory phase the animal may return to the initial phase, when (temporarily) satiated by food or ejaculatory activities, but it may also enter the second phase immediately again if satiation (= 'negative feedback'-signals) did not occur sufficiently.

In Figure 1 the arrows indicate the number of transitions from and to the successive behavioral phases. At the left side, it is shown that in the early initiation-phase behavioral transitions occur frequently (70%) towards other behavioral sequences. Early in phase 2 a considerable number of transitions (about 40%) still occurs in a direction not leading to the expected consummatory phase, but later in the appetitive phase such an exit-choice is made in less than 10% of the transitions. For that reason we have coined the term Funnel-Model to

describe the sequential organization of behavior, because it suggests that the possibility to choose for another behavioral goal becomes more and more restricted. In the laboratory situations studied, 50% of the animals, entering Phase 2, continued towards the appropriate consummatory elements, apparently after some point of no return. The animal had no choice other than completing the sequence and only after completing the total sequence, the animal could either repeat a part of Phase 3 (15%), or enter Phase 2 again (35%) or, under our experimental conditions, enter Phase 1 again (50%). We consider an animal behaving in Phase 1 as least constrained, meaning that all behavioral options are open depending on the internal state and the external stimuli, and that an animal at the very end of Phase 2 is most strongly constrained, and virtually bound to finish the complete sequence by performing the mostly reflexive acts composing the consummatory phase 3.

This Funnel-concept was strongly supported by the, mostly disturbing, effects of electrical stimulation of the

ventromedial hypothalamic nucleus (VMH). During the 30-sec stimulation periods, animals did not or hardly entered phase 2. When, however, stimulation happened to start at the very end of Phase 2, animals seemed to finish the sequence as quickly as possible. During VMH-stimulation at the end of the sequence, animals never returned to phases 2 or 3, but immediately entered a vigilant version of Phase 1, remaining there during the 30-second intermittent stimulation period [29-31]. The Funnel-shape of the behavioral progression during a sequence plays an important role in a wider context of animal behavior: coping mechanisms and behavioral states. Considering feeding, sexual behavior and agonistic activities as just three of a variety of possible behavioral sequences, we wish to address two aspects specifically: on the one hand, goal-directed behavior asks for perseverance for a specific goal, and the performing animal should not be diverted by irrelevant external or internal factors for a while. Behavioral funneling supports the animal to stay in a given behavioral sequence or behavioral state, to stay on track until the goal is reached. On the other hand, less constrained periods, like Phase 1 in between specific behavioral sequences, are necessary as switching points in order to allow the animal to choose another behavioral strategy, for entering other states and/or to pursue other goals. The funnel-shape reflects these opposing characteristics in a continuous flow of behavioral performances. β -END appears to be involved in this behavioral flow and the switching points (see sections 3.1 and especially 3.2).

Towards a general role of β -endorphin

Over the last decades, numerous reviews have appeared on the behavioral and physiological aspects of β -END [35-63]. From these, it becomes clear that β -END is involved in a wide variety of functions ranging from the cellular to the behavioral level. Many reviewers discussed the placebo effects possibly occurring on the administration of β -END and other substances influencing the μ -receptor [64-70]. Several of the mentioned reviewers of the effects of β -END proposed unifying concepts to embrace this variety into a general behavioral function, but their proposals seem to be pointing in different directions.

In 1982 Henry assumed that all general effects, for example those affecting the pain-regulating systems in the spinal cord, were induced by circulating opioids [71]. The paper did not yet consider the possibility of β -END messages via the CSF. Henry asked, however, special attention for the possibility that “the activation of a number of functions together may be due to a global activation of opiate receptors throughout the CNS”, which is consistent with the main thesis of our present paper. In the summary (p 239), after comparing the effects of stress, and sexual activities with vigorous dancing and states of

trance, Henry concludes that mild activation of the β -END system induces a state of well-being, while stronger activation results in analgesia and euphoria. On the other hand, “when the endorphin system is hypoactive,, an increased drive ensues to satisfy a deprived state, whether this is an appetite for food, water, social contact, or sexual satisfaction, etc.” [71]. This paper contained the clear hypothesis that the effects of endorphin depend on the activity state of the endorphin system. In 1984, Akil *et al.* concluded that “The multiplicity we behold in studying endogenous opioid function is dizzying”, [72], focusing in their review mainly on stress, analgesia and cardiovascular control mechanisms. In 1985 the role of β -END in learning and memory processes was addressed [73-75]. Izquierdo and Netto showed that “a variety of behavioral experiences activate the β -END system, apparently as a result of novelty; that this activation is mediated by the septo-hippocampo-subicular system; and that this seems to play a role in regulation of the retrieval of learned behavior” [74]. Due to its rather long recovery time, the arousal of the β -END system “must be reserved for events that are particularly striking to the animal”. “ β -END may obviously play a very important role in adaptive behavior” as well as in developing (alternative) coping strategies (*ibidem*).

In 1986 the μ -receptor system was discussed [59]. After referring to a variety of behavioral and physiological effects, as described in the literature, Panksepp continues as follows: “Although many of the behavioral effects could be subsumed by the principle that opioids elaborate pleasure or habit processes in the brain, such a perspective would not explain the peripheral physiological effects of opioids. Suppose we broaden the scheme and postulate that the global function of opioid systems (μ and perhaps δ) is to counteract the influence of stress. Although stress is a construct beset by serious operational and conceptual difficulties, if we consider any major perturbation of physiological homeostasis to be a stress, with opioid arousal being a cardinal counteracting influence, most effects reported for the opioid system fall into place” [59]. “The desirable affective effects of opioids can be understood as the psychic component of a brain process that helps return activity in perturbed neural circuits back to normal”. In addition, “there is an arousal component to opioid action in the brain, especially on cells of the mesolimbic DA (dopamine) pathways, which appears to elaborate the euphoric effects of opioids”, possibly to “promote homeostasis-sustaining behaviors”. “Pleasurable opioid arousal invigorates those active post-homeostatic behavior patterns such as rough-and-tumble play, that are expressed fully only when other bodily needs have been fulfilled” [59]. After some final remarks concerning stress-induced-analgesia, Panksepp concludes that “Perhaps stress-

induced-analgesia would be more properly called relief-correlated-analgesia”.

Some years later, Herbert summarized the functional aspects of β -END as follows: this peptide “is particularly concerned with regulating reproductive physiology and is part of the mechanism whereby reproduction is controlled by (and thus responsive to) various elements in the external environment, including social and physical stress” [38]. Central β -END is released during various forms of stress and “is a prime example of a peptide whose principal function seems to be *to inhibit responses in conditions under which they would be disadvantageous*” (p 739; emphasis is ours). “ β -END-containing systems can be accessed by changes in either the physical or social environment that signal adverse conditions for reproduction. The result of activation of this system is a common one: suppression of reproduction” [38].

At first sight, the comments of these successive reviewers may seem difficult to reconcile. However, taking the idea of a main role for β -END in creating a general state of well-being and pleasure (up to euphoria and trance) as a starting point, the differences between the reviewers tend to disappear. This state can be contrasted with alternative states like stress and a variety of motivational states. As proposed by Panksepp, a variety of stressors may induce perturbed neural circuits, and changes towards an opposite preferred endorphin state can be described, supported by activation of the mesolimbic dopaminergic pathways, creating reward when approaching the desired state. Basically, this is not much different, however, from what happens when an animal returns from a specific motivational state (hunger, thirst or sexual arousal) to a state of satiety and homeostatic balance, after performing the appropriate behavioral sequence [30,31,38]. Such motivational states may be the result of serious homeostatic needs, which can be very stressful. Concerning food intake, this may imply that eating may be increased or decreased to reach the preferred weight level. We suggest that β -END influences brain-activity towards a state of balance and well-being. In order to keep the brain in this preferred state, β -END apparently allows the animal to perform feeding and drinking activities (see below) as well as social grooming [76], which relieve stress and may restore a disturbed balance. Breeding activities, however, under non-optimal conditions, that would seriously disturb the state of well-being, are apparently inhibited [38,77,78], just like painful stimuli that have to be avoided [71,72,79]

Our conclusion concerning the general role of β -END is therefore the following. On the one hand, β -END may allow and stimulate behaviors that normally restore a state of homeostatic balance and well-being, and on the other hand it may inhibit behavioral changes that potentially disturb this preferred state. On the basis of this

statement, several interesting and specific questions can be raised about the behavioral effects of β -END, about specific behavioral transitions, (as studied by Herbert *et al.*) [71,72,79-85], as well as the effects of meditation. These will be discussed in the next sections.

Behavioral regulation by β -Endorphin

Regulation of food intake

The POMC neurons in the ARH are strongly involved in the regulation of food intake, at the sensory side equipped with specific receptors and at the effector- side with mechanisms controlling food intake. Most of the POMC-neurons express leptin receptors [86,87], while processing of the POMC-derived peptides is regulated by energy balance [87-90]. On the effector side, it is fully clear that hypothalamic POMC-neurons play an important role in the regulation of food intake [86,90-97]. Among the POMC-derivatives, alpha-melanocyte-stimulating hormone (α -MSH) appears to be the main one, exerting an inhibitory effect on food intake as shown in human as well as animal research, via the melanocortin receptor types MC3 and MC4 [90,92,94,95,98-103]. The role of β -END in food intake regulation appears to be less prominent and more modulatory in character. From the earliest studies on, it became clear that central administration of opiates, among them β -END, had a stimulating effect on food intake [105-112]. The stimulating effects of other neuropeptides, like galanin (GAL), were also mediated by β -END release [113] while on the other hand serotonin seems to play a role in the feeding effects of β -END [114-116]. Several recent findings have complicated the role of β -END in food intake. Its levels in both CSF and plasma were elevated after intake of palatable sucrose solutions in rats [117], while ingestion of a fatty meal induced neuronal activity in the β -END neurons, apparently after oropharyngeal stimuli arriving via the glossopharyngeal nerve [118]. This finding is in agreement with an earlier observation showing that, in the rat, β -END plays a special role in the hedonic preferences for dietary fat [119]. In addition, β -END deficient mice are less willing to work for palatable food, suggesting motivational changes in the appetitive phase [120].

Maybe, the short-term effects of β -END on food intake are different from the long-term effects, since intracerebroventricular (icv) infusion of β -END in rats stimulated food intake but chronic infusion did not sustain these stimulating effects [104]. Recently it was also observed in transgenic mice, that that short- and long term effects on POMC-neurons may be different. The long-term effects seem to be more complementary to the general POMC-effects [120,121]. After a temporary initial increase, male rats showed a lower level of food intake after a few days of chronic icv β -END administration

[122]. This weakly inhibitory effect is in agreement with results obtained from β -END-KO mice, which gained an additional 10 – 15% of body weight compared to wild-type controls. These KO mice showed an increase in food intake without changes in basal metabolic rate. The increased body weight consisted completely of an increased amount of white body fat and was only observed in male mice, not in females [121]. Finally, it has been suggested already in the early nineties [123-126] that the role of β -END in food intake is mainly sustaining, instead of playing an initiating role.

The question that has to be raised now is: How far it is possible to integrate this variety of findings into a general role for β -END in the regulation of food intake? The short-term effects of β -END seem to be most prominent and decrease the appetite-inhibiting effects of α -MSH [104] or a preceding stressor [102] and thereby β -END may play a special role in the appetitive phase of feeding behavior. These effects can be linked to the reward system which induces positive feedback stimuli in the appetitive phase [127-129] to sustain food intake of palatable food [119,121,126]. Apparently, “ β -END selectively affects a motivational component of reward behavior under non-deprived conditions” and “in the appetitive phase, β -END release increases the incentive value of food as a primary reinforcer” [120]. These behavioral effects certainly contribute to restore a state of well-being, as postulated for a general role of β -END. The question as to how far the long-term effects of β -END, consisting of moderate inhibitory effects on food intake, contribute to long term body homeostasis and weight regulation (only in males), or whether these have to be considered merely as a side-effect of β -END supporting some other POMC-derived peptide(s), remains open for further research. In conclusion, the central effects of β -END on food intake are modulatory and play a main role in the introductory/appetitive, goal-directed phase of feeding behavior. In this phase behavior can be most easily adapted to obtain or preserve a preferred state [30,31] or to choose an alternative coping strategy.

Sexual behavior

Despite the fact that the effects of opioid administration have frequently been described as reaching an orgasmic state of euphoria, the effects on sexual behavior are generally inhibitory [130]. The acute and long-term effects turned out to be complex [131-133], including those of β -END, which plays a role in male as well as in female sexual behavior. In the male, β -END is involved in the regulatory control of testosterone, via luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) mechanisms. The effects are mainly inhibitory [132,134-137]. The details of the observed effects were, however, complex [131,133,138], rather variable, for instance those

on ejaculation latencies and of naloxone [134,139-142]. Also the effects of ejaculation, and erotic stimuli (in humans) did not lead to consistent results when measuring the peripheral β -END levels [132,143-147].

Similar to what we have discussed for the control of feeding behavior, several findings suggest that β -END plays an important role only in specific phases of sexual behavior, especially the precopulatory, appetitive phase. In 1981 Meyerson observed that after icv administration amicable contacts between animals increased whereas sexual responses were decreased [148]. Later studies supported a specific role of the μ -receptors in pair-bonding [149]. Numerous studies have reported the deteriorating effects of stressors on male sexual performance [150-155]. In addition, the analgesic effect of copulatory activities has been noted repeatedly [147,156-157]. All findings, taken together, strongly suggest that the main role of β -END is played in the appetitive, precopulatory phase of sexual behavior, to pave the way for the copulatory activities themselves. In this phase, the dopaminergic system is also involved, providing a rewarding basis for the ongoing activities. The effects of β -END during the appetitive arousal state are related to its stimulating effects on the reward systems and an important role, especially in the medial preoptic area (MPOA) [130,131,133,158-172]. In 2004, it was shown that sexual behavior and especially sex-associated environmental cues activate the mesolimbic system in male rats. This activation induces internalization of μ -receptors in the MPOA within 30 minutes after mating and this internalization was still evident about 6 hours later [168,173]. Naloxone prevented this internalization but not the concurrent Fos- expression of the MPOA-neurons [173]. In 2007, it was shown convincingly that POMC-neurons in rats were activated by the arousal aspects and not by sexual activities themselves [167].

These findings are in full agreement with earlier suggestions concerning the effects of β -END on interpretation and impact of environmental stimuli [174,175]. Moreover, these findings suggest that the neural mechanisms involved in either the arousal/precopulatory phase or the copulatory phase of male sexual behavior show some fundamental differences. In the rat, an initial appetitive, precopulatory phase of approaching and investigating the female, is usually followed by a sequence of copulatory activities (mounts and intromissions) eventually leading to an ejaculation [176]. After a post-ejaculatory interval of several minutes, the whole behavioral sequence may start again. (See Figure 1 for an overview of the behavioral sequence.) β -END seems to play its specific role especially in the appetitive arousal phase (and in the post-ejaculatory period), but not during the copulatory activities themselves.

Support for the idea of ‘phase-specific’ effects of β -END was obtained by the group of Herbert [38]. They

injected β -END bilaterally by micro infusion via brain cannulas into several specific rat brain areas and made some striking observations. After showing the generally inhibiting effects of β -END and the involvement of different brain areas [80-82], it was observed that the inhibitory mechanisms of the MPOA and the medial amygdala (MeA) were very different, but had eventually the same effect. In both brain areas a specific behavioral transition in the usual sequence of (pre)copulatory events turned out to be of crucial importance: the transition between the appetitive, precopulatory, phase and the copulatory phase turned out to be important for the β -END control. After β -END administration into the MPOA, investigative activities were normal but the males never entered the copulatory phase, unless the β -END administration started after the initiation of the copulatory activities. In that case, these were performed as usual. When, however, a new female was introduced, the same precopulatory-copulatory transition was blocked again [38,85]. On the other hand, the same behavioral transition turned out to play a similar important role in the MeA, but in a completely different way. Now the precopulatory phase was completely suppressed by the β -END administration and the animals never made the transition to the copulatory phase. However, copulatory activities themselves were completely normal, as observed when β -END was administered in the later copulatory phase [38,83,84]. These transition-effects were not caused by sensory (olfactory or visual) disturbances possibly induced by the β -END infusions [38].

Apparently, the transition step between precopulatory and copulatory phases of masculine sexual behavior is under β -END control and copulation can be effectively blocked by either prevention or an endless continuation of investigative activities. Since the MeA, especially its posterodorsal part, receives genitosensory as well as olfactory information, and since it is reciprocally connected to the MPOA [31,32,177-185], this part of the neural circuitry not only plays a role in the induction of the post-ejaculatory interval, but may just as well be involved in the general control of ejaculatory activities. Manipulation of a specific but crucial behavioral transition is an extremely efficient way to induce or block the occurrence of specific parts of behavioral sequences! Herbert concluded from these and other studies that β -END "is a prime example of a peptide whose principal function seems to be to inhibit responses in conditions under which they would be disadvantageous" [38] (p 739). In our view, β -END appears to play a dual modulatory role in male sexual behavior. On the one hand it facilitates the appetitive phase by reducing stress and potential pain and by activating the reward system [130,131,133,156,165], on the other hand by inhibitory effects on specific transitions in the regular copulatory

pattern in addition to short-term- (post-ejaculatory refractory period) or long-term- (stress, seasonal effects) suppression of reproductive activities. Since the copulatory phase itself is hardly influenced by β -END, these behavioral effects fit a more general anti-stress-function: facilitating behavior towards a state of well-being, reward and even euphoria but inhibiting behavior under inappropriate, potentially stressful, conditions. This dual role of β -END on male sexual behavior is rather similar to what we concluded about its role in food intake.

In the female, β -END mainly has an inhibitory effect on receptivity, lordosis behavior and reproduction [40,132,186-193]. This inhibition occurs via the GnRH system in the medial preoptic area, which receives numerous β -END contacts [137,193-211], as well as via additional μ -receptive MPOA neurons [137,168,212-217]. Obviously, the inhibitory effects are estrogen-dependent [168,193,218-222], but additional neuroactive substances are also involved in its regulatory control, like neuropeptide Y (NPY), GAL, serotonin (5-HT) and GABA [168,195,223,224]. Interestingly, however, icv-studies showed that β -END could have also a facilitating effect on lordosis, given the proper conditions and location. In ovariectomized rats, primed with estrogen (and progesterone) lordosis in response to male mounts was only inhibited via high-affinity μ -receptors, but facilitated via low affinity δ -receptors [132,186]. The facilitating effects of β -END were restricted to the first 6 hours after estrogen administration [193,194-199]. This facilitatory effect changed into an inhibitory effect over the next 6 hours of estradiol-benzoate (EB)-priming [193,196-199,225]. The mechanisms involved were determined to be not only time-dependent but also location-dependent. If crystalline EB was implanted in the septal-preoptic regions, β -END effects were facilitatory, if implanted into the ventromedial hypothalamus the EB-implant had an inhibitory effect, while at the level of the mesencephalic reticular formation no effects were observed [225]. In 1997, Gorzalka and coworkers showed that the effects of β -END administration on lordosis were ventricle-dependent: in the lateral ventricle it worked facilitating, but in the 3rd ventricle it had an inhibitory effect, probably due to the activation of different populations of opioid receptors [226]. This observation is reminiscent of other location-dependent effects, as observed by [225] but Gorzalka *et al.* also noted that β -END had no effect on proceptive behavior, like ear-wiggling [226]. This observation is especially interesting, because it suggests again a phase-specific effect: that β -END may have differential effects on the early introductory/arousal phases of female sexual activities compared to the succeeding copulatory phase. These differential effects are reminiscent of our earlier discussion for male sexual activities, but it is obvious that additional information is

needed. In conclusion, the effects of β -END on female sexual behavior appear to be modulatory, as in the male. Depending on the brain areas affected and the state of the opioid receptors involved as well as the gonadal state of the animal, β -END may have facilitating or inhibiting effects on lordotic behavior. In how far these effects contribute to a state of well-being, as suggested for the male sexual activities, deserves further experimental attention, but the avoidance of inappropriate breeding conditions, as hypothesized by Herbert [38] certainly contributes to this state.

Reward and meditation

β -END is known to induce euphoria and to have rewarding and reinforcing properties [71,227,228]. Numerous recent reviews discussed the involvement of mu-receptors in the liking and wanting aspects of food reward as well their role in a variety of eating disorders [229-246]. Concerning the rewarding aspects of sexual behavior and the involvement of opioids, a similar series of papers and reviews is available to support this functional relationship [166,167,247-254]. The bidirectional interactions between the opioid systems, including β -END, and the mesolimbic (and incerto-hypothalamic) dopaminergic systems compose the neural substrate for the rewarding effects of eating and sexual behavior. These interactions can be considered as crucial components of the mechanisms involved in motivational drives and goal-directed behavior. The motivational effects of numerous neuroactive substances are mere reflections of their inhibitory or excitatory actions on this dopaminergic reward system, extending between the ventral tegmental area (VTA), the nucleus accumbens and the MPOA. "The (induction of a) reward state in males and females is mediated by opioids and the medial preoptic area of the anterior hypothalamus is a crucial site for sexual reward" [249,255].

In addition to the natural rewards obtained by specific behavioral actions, numerous drugs are able to influence this reward-system directly or indirectly without any specific behavioral activity. These substances induce drug-seeking behavior and addiction with all of their deleterious consequences for the individual and society [227,228,240,256-259]. β -END plays an eminent role in addiction because of its mutual modulatory relationships with the mesolimbic dopaminergic system [256,268,260-267]. Its rewarding role in cocaine, alcohol and nicotine addiction is fully supported by the presently available evidence, while the evidence for a role in addiction of tetrahydrocannabinol (THC), the psychoactive component of marijuana, seems to be more circumstantial as yet [228,257,258,261,268]. Concerning addiction-related stress control, β -END seems to play a prominent but complicated role in the

successive phases involved in addiction [228]. While enhancing the rewarding properties of the addiction-related behaviors, β -END diminishes the activity of the stress-related circuitry, (involving the locus coeruleus and the CRH-neurons in the paraventricular hypothalamic nucleus), induced by the anxiogenic side-effects of cocaine [269-273] or by unpredictable distress [273,274]. The extinction-phase, as a stressful transition between the maintenance- and the withdrawal phases [228], induces again a tremendous increase in β -END release in the nucleus accumbens [276]. During the withdrawal phase, drug desire (craving) remains high while levels of β -END are steadily decreasing [228,268,277-279].

Generally speaking, the role of β -END in reward and addiction can be described as follows: on the one hand it may enhance the initial rewarding properties of the (new) behavior or drug, while on the other hand it softens the stressing side-effects of the drug use or other aspects of the addiction-related behavior. Maybe these roles can be considered as the two sides of the same coin, because of the mutually-inhibiting effects of the reward circuitry versus the stress circuitry [280]. However, several findings suggest that the relationship between stress and reward is more complicated than a matter of mutually inhibitory circuitry. In fact, the relationship shows a remarkable similarity to the biochemical aspects of the adrenal stress response, where adrenalin serves the function of making all bodily reserves available for handling the challenge, while at almost the same moment the corticosteroids start their, partially counteracting, anabolic activities for restoring the homeostatic balance in order to be able to cope with future challenges [281,282]. We assume that a similar balanced relationship is also effective with β -END if processes related to addiction activate the stress-circuitry.

Generally, the neuronal circuitry activated by stressors involves such brain areas (or parts of) as the nucleus of the solitary tract, the parabrachial nuclei, the locus coeruleus, the central amygdaloid nucleus, the bed nucleus of the stria terminalis, the hypothalamic paraventricular nucleus, the hippocampal formation and cortical areas such as the insular and anterior cingulate regions. Depending on the nature of the stressor, physical or psychogenic, the brain areas mentioned may play a more or a less prominent role in activating the neurons of the pituitary-adrenal axis via the corticotropin-releasing-hormone (CRH-) neurons in the paraventricular nucleus of the hypothalamus [283-285]. For example, in the case of physical illness, the lower brainstem areas may play a more prominent role than during chronic, psychogenic stress [286-290]. To complicate matters even one step further: substances like ethanol also play a role in these interactions, as they have been shown to influence anxious

behavior, behavioral despair and the effects of stressors on the tail-suspension test or on novelty-suppressed feeding in mice [102,281,291]. These interaction-effects are too complicated to discuss them further here, but they show convincingly that β -END is directly or indirectly involved in a range of behavioral effects (feeding behavior) and physiological effects (adrenal size).

Apparently, a CRH-dominated stress circuitry is activated under various circumstances. While it has been observed that CRH in the CSF regulates the expression of the μ opioid receptor [292], the nociception related endothelin system is regulated by β -END levels in the CSF [293]. Interestingly for the present review, however, are the numerous observations showing that activation of the CRH-neurons induces almost immediate activation of β -END neurons, inhibiting further release of CRH [268,269,271-273,294-319]. This suggests that, similar to the ameliorating effects of the corticosteroids on the release of adrenalin, β -END is invoked immediately to modulate the maladaptive effects of the neural stress response. Activation of a rewarding feel-better-circuitry would be most effective to counterbalance stressor-effects, not only for suppressing pain (see below) if necessary to escape a predator, but also to cope with minor daily and repetitive challenges. Apparently, the neural circuitry involved is a complex mix of neuronal and CSF-signals.

Meditation has been shown to be very effective to counterbalance stress effects throughout the ages and its effects clearly stimulate the levels of β -END [296,297,307]. The central CSF-levels have not been measured yet under these circumstances. In a recent paper, however, studying ecstatic meditation using functional magnetic resonance imaging (MRI) and electroencephalographic techniques, it was observed that not only superficial cortical brain areas are involved in the effects, but that activation of the reward-system (the dopaminergic fibers contacting the accumbens nucleus) also occurs [294]. This suggests strongly that central parts of the CNS are involved in the effects of meditation, but additional supporting evidence is certainly needed. In the last 2 years, more than 100 papers have appeared about the effects of mindfulness-based stress reduction, that is inspired by vipassana meditation coming from Buddhism, on a variety of symptoms related to chronic pain, anxiety disorders, depression versus well-being and several other medical symptoms like fatigue, fibromyalgia and insomnia [306,309-326]. Although these stress-counteracting approaches show large differences in the way mindfulness is practiced [319], and are drifting away from classical mindfulness [327], obvious effects on the neuronal substrate have been observed, using a variety of techniques [314,319,328-336]. We conclude that meditation is an effective means to manage stress [280] and that β -END is extensively involved in the balance between

the positive and relaxing effects of activation of the reward circuitry and the negative consequences of physical problems, pain and (chronic) stress [337], shifting the balance in a positive direction, in accordance with our hypothesis as developed by Panksepp [59,338-344]. The euphoric state, with a total neglect of bodily and environmental cues including complete suppression of pain [71,79] can be considered as the most extreme condition in the regular balance between the brain-states and circuitries related to stress and stress-relief.

Pain control mechanisms

The extremely potent analgesic effects of β -END were discovered early, [350-355] and during the late seventies, eighties and early nineties an extensive series of publications appeared in which CSF-levels of β -END were measured and correlated with the pain levels experienced by patients and experimental animals under a variety of painful conditions. This surge of interest emerged from the finding that the analgesic effects of β -END were obvious only after icv-, and not after iv-administration [348,351-355]. This difference illustrated clearly the relative effects of the rather impenetrable blood-brain-barrier combined with the almost 3 times shorter half-life of β -END in the blood versus in the CSF (about 37 min vs. about 97 min; [355]). Despite the originally high expectations, it turned out that the correlations of central β -END levels with chronic pain states were weak or negligible [356-364] with a few exceptions related to abdominal pain and migraine, where CSF-levels tended to be lower than normal [365-372]. While these essentially negative findings make it impossible to use CSF-levels of β -END as a parameter signaling pain perception, there is no reason to conclude that CSF- β -END levels do not play a role in pain control [373].

From the beginning it was established that not only icv-administration of β -END [354,355] but also electro- or magnetic stimulation [346,374-397], electro-acupuncture [380-397] as well as physical exercise or therapy [398,399] induced strong analgesic effects, by elevating the levels of β -END in the CSF. Since acute painful stimuli also raise these CSF levels considerably [170,359,375,400,401], it is fully clear that the central release of β -END forms part of an antinociceptive system controlling pain [71,79,402,403]. It has been observed that mindfulness meditation modulates pain perception as well, e.g. [320]. This antinociceptive system includes the arcuate hypothalamic nucleus (ARH), with its content of POMC-neurons, the periaqueductal gray region [390,404,405] and several caudal brainstem areas, including the caudal raphe nuclei, from where 5-HT projections descend into the spinal cord [402,403]. Many experimental data show, however, that this system is not limited to a set of (partially reciprocal) neuronal connections but that β -END, released

into the CSF to go with the flow [14,404,405], plays an important modulating role.

As early as 1982, James Henry argued that the variety of conditions under which β -END is released and the fact that these conditions exert effects on a number of systems together, requires a global activation of opiate receptors throughout the CNS [71]. At the time, blood-borne opioid hormone, released by the pituitary or a pituitary-controlled peripheral gland to enter the CNS and the CSF, appeared to be the most appropriate candidate to induce such a generalized response [71,79]. Later studies, however, showed that β -END can also be released locally in peripheral tissues, to control (local) pain [177,179,181,406-408]. Peripheral levels of β -END may influence the spinal cord [5,71], but brain-CSF levels arise from the arcuate hypothalamic nucleus (ARH) as well as from numerous terminals surrounding the ventricular spaces and are sufficiently high to induce the central effects. The following findings provide additional evidence.

Extracellular levels of β -END in the ARH show two to fourfold increases upon painful or 5-HT stimulation. While this release may potentially activate all neighboring POMC neurons, the destination will be the adjoining CSF [404,405], to 'go with the flow'. The flowing CSF may collect additional POMC and β -END from the many varicose fibers running subependymally alongside the ventricular system. It is therefore not surprising that high levels of β -END have been measured in the CSF after stimulating its release by a painful or an electrical stimulus [170,374,375,377,409-412] CSF-levels increased 20-fold, after this central release and the analgesic effects were clearly correlated with the duration and the increase of the levels. In 2001 Shen [379] reported an elucidating rabbit experiment. CSF from one animal, after 30 min of electro-acupuncture, was infused into the lateral ventricle of a naïve recipient rabbit. The analgesic effect was observed in the recipient rabbit, showing that volume transmission via the CSF can indeed be effective. More recently, Zubrzycka and Janecka, showed in an experiment involving both tooth pulp- and central gray electrical stimulation, that β -END was released into the CSF after tooth pulp stimulation and this release could be inhibited by the PAG-stimulation [405,412]. They concluded that 'endogenous β -END, released as a result of electrical tooth pulp stimulation in orofacial pain, diffuses through the cerebroventricular ependyma into the CSF and exerts a modulatory effect, mediated by μ -receptors, altering the properties of neurons in the trigeminal sensory nuclei, interneurons, and motoneurons of the hypoglossal nerve' [405].

Additional evidence comes from intranasal (IN-) application studies, showing that a large variety of substances follow direct nose-to-brain pathways to enter the brain cavity and the CSF compartment, generally within a few

minutes [22]. For β -END itself the effects of IN-administration have been hardly reported, probably because of its adverse effects on the nasal epithelium [413,414] Only in an older monkey study clear-cut effects of IN- β -END were reported, in this case on induced prolactin levels [415]. Several substances supposed to elevate central β -END levels: desmopressin, [416] and calcitonin [417,418] have been tried with variable results and without measurement of CSF-levels. Intranasally applied morphine, however, has been shown to reach the ventricular system of rodents within minutes with a clear distribution advantage over the intravenous and especially oral administration levels [419,420]. Peripheral levels apparently played no role in the elevated brain levels. Several substances are currently applied intranasally for clinical pain relief, especially fentanyl [416,421-426] and the opioid system and the CSF as the transport medium seem to be always involved in the effects of such substances. In addition to mechanisms introducing substances into the CSF, it has also been observed that specific ependymal cells and other neurons are able to take up and transport specific substances from the CSF, towards the soma of neurons, frequently located far away from the ventricular surfaces, where they may elicit responses leading to changes in gene expression [427-429].

Already mentioned were some studies in which transport via the CSF seems to be the only possible explanation of the observed effects. Yadid *et al.* observed a strong reduction of pain behaviors after transplantation of adrenal medullary cells into the subarachnoid space of the spinal cord [430,431] but there were several reasons to assume that the observed effects were not the local effects of the transplant. In 2000, Yadid *et al.* showed the involvement of central β -END mechanisms and the arcuate nucleus in the observed analgesia, apparently by releasing β -END via the CSF as a transporter of messages [411]. In another interesting study, Finegold *et al.* transferred genes to the meninges surrounding the spinal cord, upon which pia mater cells started to produce β -END [432]. This pia mater-release of β -END had a clear analgesic effect on an inflammation model of persistent pain. Their paracrine paradigm for the treatment of chronic pain shows that substances released in the CSF become functional when transported via the CSF. In conclusion, β -END plays a complicated but major role in the mechanisms controlling pain, and transport via the CSF (volume transmission) forms an essential part in these effects [14]. This role is in full agreement with the rewarding and anti-stress roles put forward in the preceding sections of this review.

Other effects of β -END

In order to limit the scope of the present review, additional behavioral, functional and clinical effects of

β -END will not be discussed in detail. Such effects have been reported, for example, on the mechanisms of intestinal transit [439] cardiovascular control [103,122,434] and the growth and metastasis of mammary tumor cells [435], but also on the immune system, complex arthritic inflammatory syndromes, fibromyalgia and cerebral infarction [180,271,436-448]. An extra complication is that the control and effects of β -END are extensively related to a variety of other humoral and neuromodulatory factors, like serotonin, involved in syndrome such as schizophrenia and depression [449,450]. For that reason, Hegadoren *et al.* called attention to a possible role of β -END in the pathophysiology of major depression [337]. They reviewed the multiple interactive links between serotonin, β -END and the HPA-axis involved in major depression. Such interactions are of great importance in view of the hypothesis that β -END is involved in anti-stress mechanisms and well-being. Perhaps the involvement of β -END in depression gives this mind-state a considerable, but undesirable, degree of stability. In that case, the stability of a depression has to be considered as an unpleasant side effect. A discussion of these possibilities is beyond the scope of the present review.

One interaction effect deserves some special attention, namely with the neuropeptide oxytocin (OT), because this peptide plays a major role in positive social interactions and because of it may be released into the CSF to influence distant brain areas by going with the flow [3,4,22]. In 1989 Melrose and Knigge studied horse brains and proposed evolutionary relationships for POMC, oxytocin (OT) and vasopressin (AVP) neurons, all of them surrounding the ventricular system and equipped with an extensive set of mutual connections [451]. The remarkable co-existence of opiocortin and corticotropin-releasing factor immunoreactive CRF-IR projections surrounding the ventricular system, as observed from the earliest studies [452,453], contributes to the suggestion of mutual interaction effects. The fact that each of these neuropeptides shows facilitatory or inhibitory effects on behavior as well as physiological mechanisms like feeding, sex, aggression, pain, reward, (anti)stress and social relationships like maternal and pair-bonding behavior, makes the conclusion unavoidable that these neuropeptides must operate in close mutual interactive relationships. Many behavioral and physiological studies support the existence of these functional relationships [14,182,454-479]. Concerning the focus of the present review, central mechanisms using the CSF for transport, readers are also referred to [3-5,14,22,480,481].

Conclusions

Summarizing the effects of β -END on brain and behavior as described in the literature, they seem to be separable into 2 categories. On the one hand, β -END, released into

the CSF, to go with the flow, may have far-reaching effects on distant brain regions involved in a variety of behaviors, related to reward mechanisms and motivational and mental states. This is the global effect with a tendency towards stress-reduction, leading to a sense of well-being by homeostatic balance and behavioral stability. On the other hand, and in addition to this state-transition-effect, local administration of β -END in specific brain areas like amygdala or hypothalamus induces specific inhibitory effects on transitions of the behavioral sequence thereby preventing the occurrence of a specific goal. A funnel-model has been introduced to describe the successive phases of a behavioral sequence. The question as to how far the specific behavioral effects always support the global effect or have to be considered as specific local mechanisms controlling specific behavioral sequences needs further attention and research. Additional experiments with local manipulation of β -END levels in specific brain regions are needed to shed more light on the complex global and specific effects of β -END on the CNS, on behavior and behavioral transitions.

Abbreviations

α -MSH: Alpha-melanocyte-stimulating hormone; ARH: Arcuate hypothalamic nucleus; AVP: Vasopressin; β -END: Beta-endorphin; CRH: Corticotropin-releasing hormone; CNS: Central nervous system; CSF: Cerebrospinal fluid; EB: Estradiol benzoate; GABA: Gamma-aminobutyric acid; GAL: Galanin; GnRH: Gonadotropin-releasing hormone; HPA: Hypothalamus-pituitary-adrenal; 5-HT: Serotonin; icv: Intracerebroventricular; IN: Intranasal; -IR: -immunoreactive; KO: Knock-out; LH: Luteinizing hormone; MC3/4: Melanocortin receptor types; MeA: Medial amygdala; MPOA: Medial preoptic area; NPY: Neuropeptide Y; OT: Oxytocin; PAG: Periaqueductal gray; POMC: Proopiomelanocortin; THC: Tetrahydrocannabinol; VMH: Ventromedial hypothalamic nucleus; VT: Volume transmission.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JGV contributed 80%, and HPB 20% to this review. Both authors have read and approved the final version of this manuscript.

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