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The neurobiology of pleasure, reward processes, addiction and their health implications

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Abstract

Modern science begins to understand pleasure as a potential component of salutogenesis. Thereby, pleasure is described as a state or feeling of happiness and satisfaction resulting from an experience that one enjoys. We examine the neurobiological factors underlying reward processes and pleasure phenomena. Further, health implications related to pleasurable activities are analyzed. With regard to possible negative effects of pleasure, we focus on addiction and motivational toxicity. Pleasure can serve cognition, productivity and health, but simultaneously promotes addiction and other negative behaviors, i.e., motivational toxicity. It is a complex neurobiological phenomenon, relying on reward circuitry or limbic activity. These processes involve dopaminergic signaling. Moreover, endorphin and endogenous morphinergic mechanisms may play a role. Natural rewarding activities are necessary for survival and appetitive motivation, usually governing beneficial biological behaviors like eating, sex and reproduction. Social contacts can further facilitate the positive effects exerted by pleasurable experiences. However, artificial stimulants can be detrimental, since flexibility and normal control of behavior are deteriorated. Additionally, addictive drugs are capable of directly acting on reward pathways. Thus, the concrete outcome of pleasant experiences may be a question of dose. Moderate pleasurable experiences are able to enhance biological flexibility and health. Hence, pleasure can be a resistance resource or may serve salutogenesis. Natural rewards are mediated by sensory organ stimulation, thereby exhibiting a potential association with complementary medical approaches. Trust and belief can be part of a self-healing potential connected with rewarding stimuli. Further, the placebo response physiologically resembles pleasure phenomena, since both involve brain's reward circuitry stimulation and subjective feelings of well-being. Pleasurable activities can stimulate personal growth and may help to induce healthy behavioral changes, including stress management. However, more research is needed to better understand the nature, neurobiology and maybe dangerous aspects of pleasure. Also, a possible involvement of endogenous morphinergic signaling has to be studied further.

INVITED NEL REVIEW

Introduction

Medicine is typically interested in disease-promoting factors and ways to cure. However, health-enhancing factors are becoming more popular, and the concept of salutogenesis and its association with self-care is of growing importance [1,2]. This may be due to money shortage in the health care system – in relation to its demands – and the rapidly increasing interest in preventive medicine and disease avoidance.

For neuroscientists, the brain most often is related to neural disorders and disease mechanisms – which are of interest, undoubtedly. But much could also be learned by studying the brain in relation to health. The brain has processes and salutogenic functions that contribute to health by enabling one's experiences in life to benefit one's health (Figure 1) [3]. Science has ever neglected positive sensations and mind states like satisfaction and contentment, solely focusing upon pathogenetic processes. For example, a vast number of publications on depression and mental disorders exist, but only a few describe possible mechanisms underlying feelings of joy and bliss.

What makes one feel good instead of bad? What are possible resources within the brain that medicine may want to use? May pleasure possibly be a concept that is available for each individual to protect from disease or serve health processes? Besides feeling good, what are the biological implications of pleasurable sensations, and what are the risks of pleasure-seeking behavior, i.e., addiction? May pleasure, at last, facilitate survival and early death likewise?

With this work we try to examine the neurobiology of pleasure and shed some light on implicated risks, health consequences and molecular mechanisms in connection with the pleasure phenomenon.

Reward and motivation

Research has identified a biological mechanism mediating behavior motivated by events commonly associated with pleasure. This mechanism is called 'reward'. It is usually governing normal behavior through pleasurable experiences [4]. Pleasure, however, describes a 'state or feeling of happiness or satisfaction resulting from an experience that one enjoys' [5]. Pleasure is a subjective phenomenon, i.e., subjective quality. Hence, an intimate association between reward and pleasure exists [4,6]. In neurobiology, pleasure is a competence or function of the reward and motivation circuitries that are imbedded in the central nervous system (CNS). Anatomically, these reward pathways are particularly linked to the brain's limbic system. The underlying physiology, however, is complex and morphological correlates are still a matter of thorough research.

Motivation may be divided into two categories – appetitive and aversive motivation. Appetitive motivation concerns behavior directed towards goals that are normally associated with positive hedonic, i.e., pleasurable, processes (food, recreational drugs, sex etc.). In contrast, aversive motivation involves getting away from hedonically unpleasant conditions [4]. Consequently, two fundamental forces rule motivation: pleasure and pain. It has been suggested that pleasure may be associated with *beneception*, events that facilitate survival and thus 'benefit' the organism or species from an evolutionary biology perspective [7]. Pain, on the other hand, is associated with *nociception*. This latter term basically describes conditions that may have undesirable biological consequences for an organism [4,7]. However, the illustrated division of pleasure and pain in reference to their possible biological functions and outcome should not lead to an incorrect understanding, since both conditions – in specific situations – may have the capacity to serve survival and 'amusement' likewise. Thus, pain and pleasure potentially merge into another. With regard to specialized brain compartments involved in motivational processes, the physiological substrate for appetitive or aversive motivation (as for reward and avoidance) primarily lies within the limbic system [8–12].

The common idea that the limbic system is solely concerned with feelings and emotion is at best a half-truth, but there certainly exists a connection which is relevant to the pleasure phenomenon [13]. Yet, the limbic system is made up of the limbic lobe and certain additional structures (Figure 2) [14]. The limbic lobe surrounds the corpus callosum and consists of the cingulate gyrus and the parahippocampal gyrus. The hippocampus, which is in the floor of the temporal horn of the lateral ventricle and is closely linked to memory processing, is also included in the limbic lobe [14]. Additional structures incorporated in the limbic system are the dentate gyrus, amygdala, hypothalamus (especially the mammillary bodies), septal area (in the basal forebrain) and thalamus (anterior and some other nuclei). Functionally, the 'hippocampal formation' consists of the hippocampus, the dentate gyrus and most of the parahippocampal gyrus [13].

Neurobiologists have long known that the euphoria induced by drugs of abuse, sex or other things we enjoy arises because all these factors ultimately boost the activity of the brain's pleasure and reward systems. These are made up of complex circuits of nerve cells or neurons that evolved to make us feel flush after eating or sex – things we need to do to survive and pass along our genes [15,16]. Reward pathways are evolutionarily ancient, like limbic structures. Limbic and reward systems share common mechanisms and morphological structures. In fact, integral CNS components involved in reward and motivational processes are of limbic origin [14]. For example, prefrontal or orbitofrontal cortices, cingulate gyrus, amygdala, hippocampus and nucleus accumbens participate in the reward physiology [8]. Thus – pleasure, limbic system and reward circuitry seem to be biologically interconnected. Memories of the pleasure of wellness, i.e., 'remembered wellness', are accessible to this circuitry through hippocampal mechanisms [14]. Further, belief affects mesocortical-mesolimbic appraisal of a pleasurable

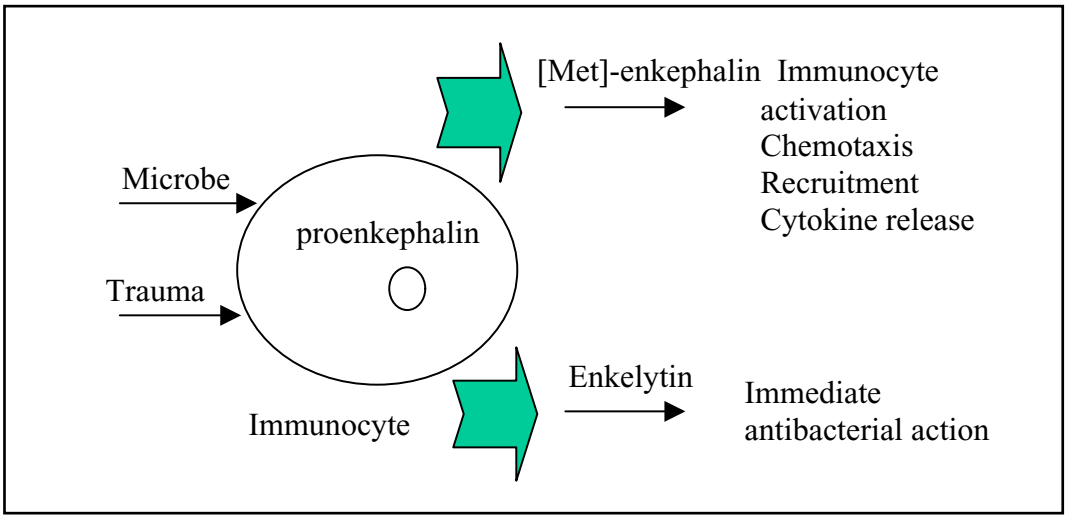

Figure 1. Opioid peptides have been shown to be involved with reward signalling in the central nervous system [140]. Interestingly, in the methionine enkephalin precursor, proenkephalin, a potent antibacterial peptide is found that is also bracketed by basic amino acids, indicating cleavage sites. Thus, when called upon both molecules will appear, i.e., trauma or pleasure, demonstrating a association with feeling good and protection [140].

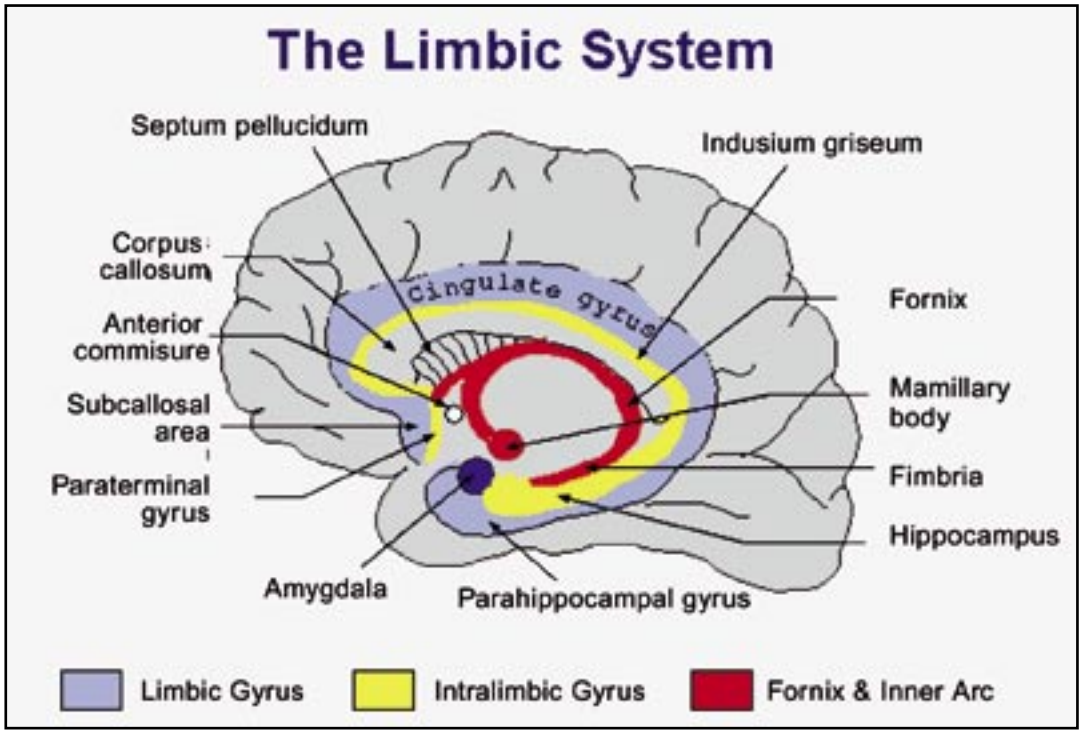

Figure 2. Anatomy of the Limbic System.

experience, leaving one, for example, well and relaxed (see below).

The same pleasant experience – like eating chocolate – may turn into an unpleasant one when a pleasurable activity is continued for an extended period of time. Interestingly, in an experiment testing this subjective quality change of an ongoing activity, the orbitofrontal cortex (OFC) proved to be a crucial but functionally segregated structure: caudiomedial parts of the OFC, in addition to the subcallosal region, insula/operculum, striatum and midbrain, were recruited when subjects eating chocolate were highly motivated to eat and rated the chocolate as very pleasant [17]. In contrast, eating chocolate despite being satiated activated the caudolateral OFC (and other regions of the brain) [17]. Accordingly, modulation was observed in cortical chemosensory areas – including insula and caudiomedial/caudolateral OFC – suggesting that the reward value of food is represented there. However, the medial and lateral caudal OFC showed opposite activity patterns, indicating a functional segregation of the neural representation of reward and punishment

within this region. The only brain region that was active during both positive and negative compared with neutral conditions was the posterior cingulate cortex [17]. These findings support the presented hypothesis that two separate motivational system exist: one facilitating approach and another avoidance behaviors [17]. Nonetheless, reward and punishment are functionally – and anatomically – closely interconnected.

A crucial component of CNS reward and motivation circuitries are nerve cells that originate in the ventral tegmental area (VTA), near the base of the brain. These cells send projections to target regions in the frontal brain – most notably to a structure deep beneath the frontal cortex, i.e., nucleus accumbens [15,16]. The essential neurotransmitter of this connection is dopamine, as described below. Clearly, the VTA or mesolimbic dopamine system represents a rather old but very effective part of motivational physiology and behavior. However, in mammals (humans), the reward circuit is more complex, and it is integrated with several other brain regions that serve to enrich an experience with emotion (as an example) and direct the individual's response or behavior toward rewarding stimuli, including food, sex and social interaction [6]. The amygdala, for instance, is a special part of limbic and reward systems that is closely related to emotion (especially fear) and has many post-synaptic receptors for which gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter [14]. Diazepam and other anxiolytics mimic the action of GABA at this site. Researchers have hypothesized that pleasurable experiences like various complementary medical treatments – e.g., acupuncture – may exert calming effects via release of GABA in the amygdala and other limbic areas [13,14]. This speculative aspect may be supported by recent findings that link endogenous morphine production to limbic structures and complementary or alternative medicine (CAM) [14]. Thus, on the neurochemical level, pleasure may involve substances that possess calming and anxiolytic capacities, thereby facilitating feelings of well-being and relaxation (see below).

The amygdala also helps to assess whether an experience is pleasurable or aversive (and whether it should be repeated or avoided) and further helps to forge connections between an experience and other cues [15,16]. Meanwhile, the hippocampus participates in recording memories of an experience, including where, when and with whom it occurred [6]. The frontal cortex, however, coordinates and processes all this information and consequently determines the ultimate behavior. Finally, the VTA-accumbens pathway acts as a measuring tool and regulator of reward: it 'tells' the other brain centers how rewarding an activity is [6]. The more rewarding an activity is deemed, the more likely the individual is to remember it well and repeat it [6].

With regard to frequent neuronal reward 'tracks' within the CNS, activation of the medial forebrain bundle (MFB), as it courses through the lateral hypothalamus to the ventral tegmentum, has been shown to produce robust rewarding effects [4,18]. Again, dopamine is involved [19]. Electrophysiological and neurochemical techniques revealed: CNS stimulation may activate a descending component of the MFB which is synaptically coupled at the ventral tegmentum to the ascending mesolimbic dopamine system, i.e., nucleus accumbens [4,6,18,19,20]. Pleasure-inducing electrical stimulation thus involves a circuitous reward pathway, first activating a descending MFB component and then the ascending mesolimbic dopamine pathway. Clearly, we can speak of brain's reward and motivation circuitries.

Taken together, the brain possesses specialized pathways that mediate pleasure, reward and motivation. Psychomotor stimulants and opiates – similar to experimental electrical stimulation – activate this reward system by their pharmacological actions in the VTA and nucleus accumbens [15,16,20]. Ventral tegmental activation, however, as well as other essential CNS reward features involves dopamine signaling. Other neurotransmitters (e.g., GABA, glutamate, serotonin, stress hormones) may play a critical role too [21,22]. In addition, endogenous morphine/opioid peptide production may be of importance (discussed below). Natural rewards like food and sex in accordance with other substances, such as caffeine, ethanol, nicotine etc., may also activate brain's reward and motivation circuitries [20].

Pleasure and addiction

Reward and motivation can be considered a natural component of normal behavior. Clearly, reward pathways serve to direct behavior towards goals that are normally beneficial and promote survival of an organism or species, e.g., food and water intake, reproductive activities [7]. These generally pleasurable actions are useful and may not constitute addiction. However, a loss of flexibility and the disability to make free decisions, i.e., extreme control of behavior, as described in addiction, may be seen as one of the distinguishing features between pleasure/reward and addiction. This addiction-related behavioral inflexibility and the impossibility of normal rewards to govern behavior may be called *motivational toxicity* [4].

Some drugs, like cocaine and heroin, quickly and uniformly exert extreme control over behavior, while others are less potent – such as moderate alcohol consumption or occasional nicotine use [4]. The most powerful drug rewards include the psychomotor stimulants (e.g., amphetamine, cocaine) and opiates (e.g., heroine, morphine). Indeed, drug influence on behavior not only depends on the amount, duration and frequency of abuse but also on the type of substance involved [15,16,23,24]. Needless to say that personality, social and genetic factors – in addition to individual differences in reward or motivation system functioning and physiology – may also play an important role [4,6,8,14,25–36]. However, drug-induced CNS effects remain the primary determinants of chemical drug addiction, whereas nonpharmacological factors are

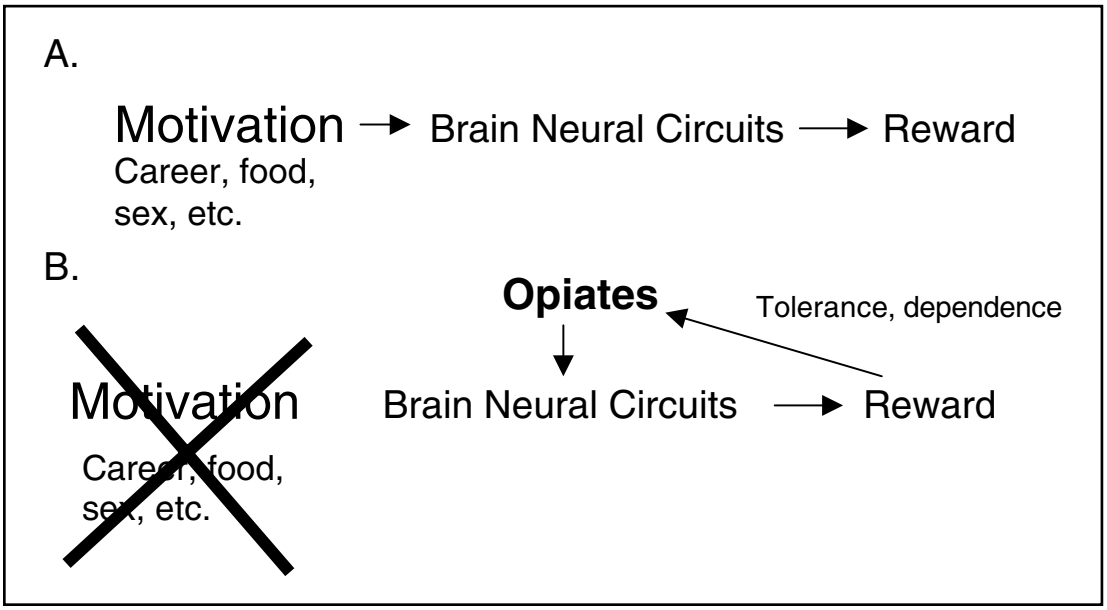

Figure 3. Individuals have conventional motivation items that depend on brain neural circuits as described in the text (A). Once these motivational items are achieved such endowed individuals feel good, i.e., reward processes. These processes in part depend on opioid and opiate signaling. If these chemical messengers are taken exogenously (B) normal motivational stimuli are lost since the same result can be achieved by bypassing these processes. However, because high doses of these chemical messengers can be taken these neural circuits become tolerant to these substances, and by the circuits' nature the individual wants to experience more artificial reward process activity, leading to higher doses and eventual dependence. Thus, substances of abuse create a short-circuit, producing reward activity at a level that was never meant to be. We surmise because this short-circuit requires not only adaptations by physiological process but molecular modifications, that some of the resulting CNS changes may be permanent.

likely to influence initial drug use and determine how rapidly an addiction develops [4,15,16]. Beyond that, gambling and other 'behavioral addictions' may involve the same reward pathways like chemical drugs [6]. The fact that chemicals are strongly capable of influencing behavior may not constitute addiction any more than the chemical reactions underlying taste, smell etc., i.e., positive or pleasurable sensations. Consequently, chemical or nonchemical reward induction may stand for ameliorating or deteriorating effects likewise, and this may account for secondary health implications (described below).

Addiction is seen as a behavioral syndrome where drugs inevitably control over behavior. It is not defined, at least in the first place, by physiological withdrawal reactions accompanying abstinence [4]. Thereby, drug abuse develops along a continuum, starting with casual or recreational use (i.e., pleasure) and ending where drugs dominate the individual's behavior (i.e., addiction, motivational toxicity) [37]. Taken together, addiction may be characterized by a loss of control over pleasurable and biologically useful events ('healthy drug use'), turning a positive motivation into a disaster.

When humans neglect formerly potent rewards like career, wealth or sex and focus their behavior on drug consumption only, they may be considered drug addicts (Figure 3). However, the pathophysiology responsible for this disruption of normal motivational hierarchies, i.e., motivational toxicity, is still speculative. While rewards normally effective in influencing behavior lose their ability to motivate an organism, deteriorated dopaminergic functions and a loss of balance (*homeostasis*) – as well as an autoregulatory inflexibility – may predominate [26,38]. Other potentially detrimental molecular mechanisms may be important too. This failure of 'healthy' biochemical signaling pathways to return to normal – resembling the chronic stress pathophysiology – may be followed by hazardous health consequences over time [10,26,39,40]. Instead of natural reward processes that promote health and survival, possibly mediated by moderate sensory organ stimulation, direct pharmacological activation of CNS reward and motivation circuitries (via drug ingestion) determines behavior [4]. Thus, motivational toxicity distinguishes drug addiction from simple stimulus or drug activation of reward mechanisms.

Activation of brain reward systems produces changes in affect ranging from slight mood elevation to intense pleasure and euphoria, and these physiological states usually help direct behavior toward natural rewards [41–44]. Some chemicals, however, bypass the sensory receptors mediating natural rewards (see above; Figure 3). In fact, caffeine, alcohol and nicotine, given as examples, all activate brain reward pathways directly. Moderate use of these substances (especially alcohol) has gained widespread acceptance. Moreover, low-dose consumption sometimes is considered healthy [45–48]. Further, some drugs are known for their recreational use, involving, for instance, desirable psychological effects – such as relaxation and

stress reduction [12,14,26]. Much like moderate caffeine and alcohol use, potent addictive drugs activate brain reward systems directly. But this activation is much more intense, causing the individual to crave the substance and focus activities solely around drug ingestion [4,6]. Thus, the ability of addictive drugs to strongly activate CNS reward systems – and to chemically alter normal functions of these systems – is a crucial feature of addiction [4,25,49,50].

The limbic system provides a neuroanatomical substrate for emotions and motivated behavior, including stress response pathways and reward physiology [10,12,14,21,51]. Moreover, the *extended amygdala* contains parts of the nucleus accumbens and amygdala, and it is imbedded in limbic activity [21,22]. Its location in the basal forebrain identifies the extended amygdala as an element of midbrain-basal forebrain neural reinforcement structures that participate in drug addiction and involve key neurotransmitters like dopamine, opioid peptides, serotonin, GABA and glutamate [15,22]. Hence, drug withdrawal is associated with negative affect and 'dysregulation' of reward pathways, i.e., *functional neurotoxicity*, possibly involving identical neurochemical processes and structures implicated in acute drug reinforcement, including the extended amygdala [22]. In addition, functional neurotoxicity may be accompanied by recruitment of stress response mechanisms, leading to continued dysfunctions in reward and stress physiology over time – i.e., chronic stress, affective disorders [10,39,40]. Persistent functional neurotoxicity, as potentially seen in chronic drug abuse, could be responsible for a long-lasting vulnerability to relapse [22]. It has been hypothesized that it may also lead to a change in set point for drug reward that may represent an allostatic state contributing to vulnerability to relapse and reentry into the addiction cycle [2,22]. Moreover, relapse vulnerability associated with functional neurotoxicity may be enhanced during acute and chronic stress [6]. The latter may be due to the fact that stress induces pleasure-seeking behavior, and during times of stress, the imaginable pleasure of initial drug use (and other positive cues related to drug consumption) is not forgotten. Stressful stimuli and/or exposure to low drug doses – as well as drug-associated cues – possibly trigger craving, and further, they may send addicts directly back to relapse [15,16]. While pleasure, in general, is capable of reducing stress or inducing stress relieving behavior, this useful strategy may turn out to be detrimental and facilitate addiction in the end [6]. Again, we see the 'double-edged sword' behind pleasure (and addiction), i.e., two sides of one medal: pleasure may be a source of biologically beneficial motivational behavior – at the possible expense of long-term consequences that may not serve health well.

With regard to neuropathophysiological mechanisms supporting addiction, we find uniform signaling pathways and common CNS activities underlying different forms of drug abuse and different subjective experiences. At the bottom, as described, lies limbic and reward system stimulation, including VTA, extended amygdala and prefrontal cortex activity. However, addiction is a complex phenomenon. Immediately after drug ingestion, feelings of pleasure, euphoria, and rush predominate (the sublenticular extended amygdala and VTA are of particular importance here), followed by induction of craving with accentuated amygdalar and nucleus accumbens activity [15,16]. The craving grows as the euphoria wears off. Moreover, initial drug exposure triggers tolerance and, in the drug's absence, discomfort that only more drug can cure [6]. Tolerance and dependence are related to a suppression of the brain's reward circuitry that, ironically, is a key feature of frequent and continued drug abuse [6,15]. Thus, the reward system fails to give rewards in the end. The situation changes, however, when drug consumption is stopped for a longer period of time. But the neurophysiology then does not necessarily return to normal, since relapse vulnerability stays – and may even grow bigger. Ultimately, following a 'successful' withdrawal, drug sensitization may take over [15,16,52]. This secondary effect of drug consumption, i.e., addiction, is associated with a characteristic pattern of cellular gene and protein production:

CREB (cAMP response element-binding protein) is a nuclear transcription factor involved in the pathophysiology of addiction (See Figure 4). When drugs are ingested, dopamine levels especially in the nucleus accumbens rise, stimulating dopamine-responsive cells to enhance cyclic AMP (cAMP) concentrations, thereby activating CREB [6,53,54]. CREB induces a specific gene expression, coding for proteins that, for example, suppress the reward circuitry (i.e., tolerance induction) [15,16,54]. One of these CREB-dependent proteins is dynorphin – a natural molecule with opium-like effects that is synthesized in the nucleus accumbens and triggers a negative feedback loop, exerting inhibitory effects on VTA neurons [6,20,55]. The increase in dynorphin also facilitates dependence, since its reward suppression leaves one depressed and unable to take pleasure in previously enjoyable activities (in the drug's absence) [6,55]. However, CREB is switched off only shortly after drug consumption has ended. Thus, this transcription factor may not be responsible for conditions that draw 'former' addicts back to substance abuse after years of abstinence. Such relapse is driven, for example, by drug sensitization, a phenomenon that sets in when drug use stops and tolerance wanes [15,16,54]. Delta FosB, a transcription factor that exerts its functions in response to chronic drug abuse, is released in the nucleus accumbens [54,55,56]. This stable protein remains active for months following drug ingestion, possibly controlling gene expression even after the cessation of drug taking [6,54]. Hence, delta FosB may cause drug addicts to become hypersensitive to drugs, leading to relapse even when only minimal doses of drugs are encountered [15,54,56]. Interestingly, it is also induced in response to repetitious non-drug rewards and may therefore represent a more general mechanism participating in reward-associated behavior change [6,15,16]. Sensitization – seen in a more positive connection

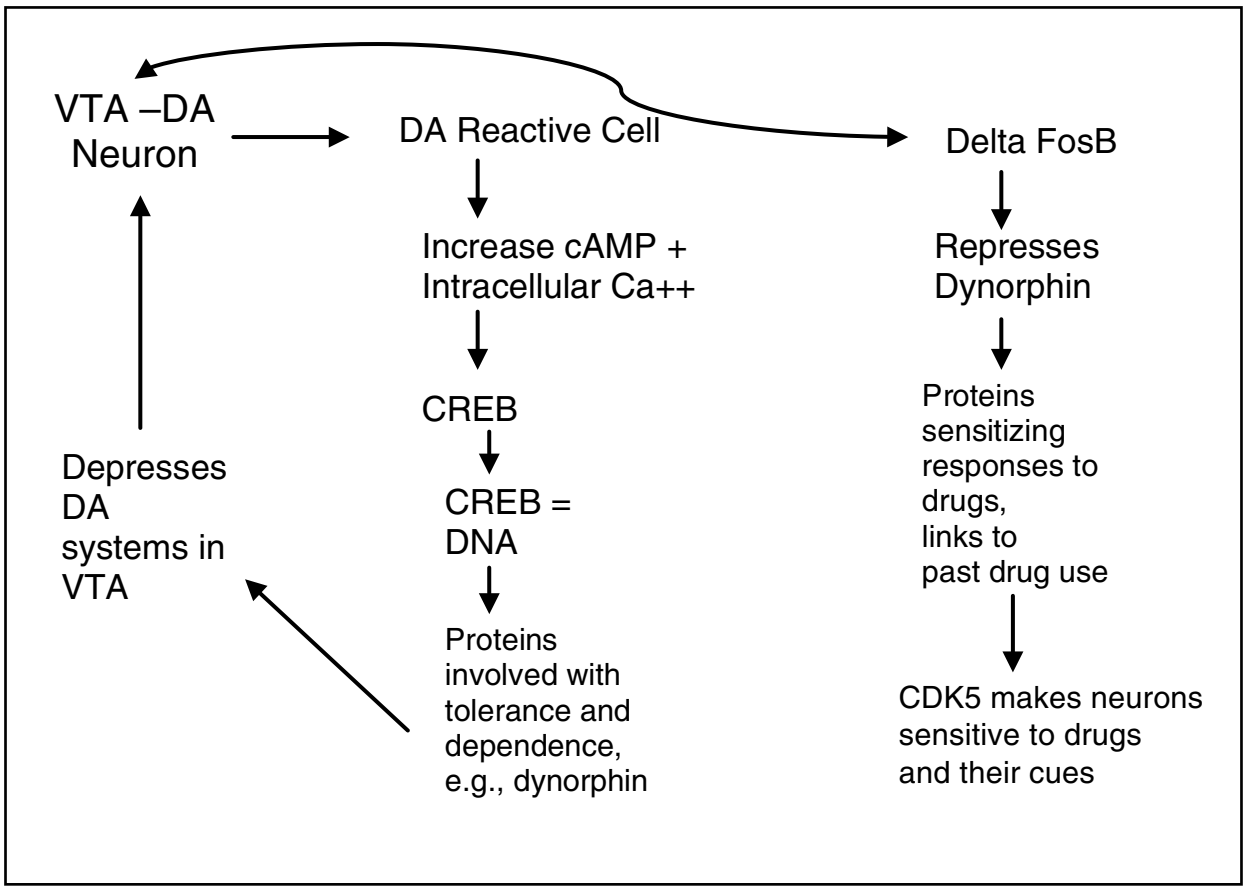

Figure 4. Dopamine (DA) involvement with ventral tegmental area (VTA) in substance abuse (Modified from [6]; see text).

– could further point out the fact that certain rewards are especially wanted by an organism, including useful (i.e., beneficial) and plainly pleasurable activities. Again, some CAM procedures may be mentioned in this context [14].

Taken together, reward circuitry alterations in the course of pleasure-seeking behavior and drug abuse potentially promote tolerance, dependence, craving, relapse and vulnerability [6,16,54]. However, pleasure is a substantial feature of drug consumption – but prolonged abuse facilitates tolerance and dependence. Due to CREB activity, sensitivity to the drug is reduced at first [6,54]. Yet, with more prolonged abstention, changes in delta FosB activity and glutamate signaling predominate [15,16,54–56]. These actions may trigger relapse by increasing sensitivity to the drug's effects (if used again), eliciting powerful responses to memories of past highs and cues that bring those memories to mind [6,15,52].

Dopamine

Dopamine is a key player in pleasure and reward physiology. However, while progress in neurobiology rapidly unfolds, we can expect other neurotransmitters to be added to this list, e.g., endocannabinoids [14,27,57]. Although substantial parts of the brain's reward and motivation circuitry have already been discovered in the 1950's, it took science over 20 years to apply this knowledge to the study of mechanisms involved in the rewarding aspects of substance abuse [58]. Within this context, opiate antagonists are capable of blocking the dopamine agonist activation of the CNS reward system [58]. Thus, dopamine and opiates/opioid peptides may be interconnected in the drug-pleasure-reward chain [58,59]. Yet, dopamine may represent a basic link of this chain.

The dopamine hypothesis, pointing out dopamine's association with neurobiological mechanisms involved in addiction, pleasure and reward (including the placebo effect), has become very popular [14,53,60]. But still we don't know all the precise CNS pathways of substances that cause pleasure. Different neuronal circuits may even overlap: The placebo circuitry, for instance, is coupled to consciousness, expectation, euphoria and gratification [53]. It may even involve physiological stress reduction and an activation of the relaxation response (the physiological counterpart of the stress response), and additionally, intrinsic placebo mechanisms may also be included in drug addiction [14,26,27,53,61]. The placebo effect, however, is complex and it may not only be mediated by dopaminergic reward mechanisms in the brain (that are related to positive or pleasurable expectations).

Dopamine has received special attention from psychopharmacologists, due to its obvious role in mood, affect and motivation regulation [4,20,53]. Although several distinct dopamine systems (i.e., receptors, receptor subtypes) exist in the brain, the mesolimbic appears to be the most important for motivational pro-

cesses [4,55]. Many drugs seem to exert their effects on behavior by stimulation of the mesolimbic dopamine activity [4,6,52]. Clearly, drugs of abuse cause the nucleus accumbens to receive a flood of dopamine (and sometimes dopamine-mimicking signals as well) [15,16]. Cells in the mesolimbic dopamine system, however, also show spontaneous activity – that is, action potentials are constantly generated at a slow rate. The result is a steady (basal) release of small amounts of dopamine into the synaptic cleft, maintaining normal affective tone and mood [4,42,62]. Moreover, some forms of clinical depression may result from unusually low dopamine levels [4,10,63]. Low dopamine may further be associated with drug consumption, since repeated use of cocaine or morphine, for example, may deplete dopamine from the mesolimbic dopamine system and reward circuitry [4,6,15]. These dopamine depletions may be responsible for normal rewards to losing their motivational significance (i.e., tolerance induction, motivational toxicity). At the same time, the mesolimbic dopamine system becomes even more sensitive to activation by psychomotor stimulants and opiates. Consequently, sensitization develops (as illustrated). Counter intuitively, abstinence from cocaine or morphine after repeated administration may also decrease dopamine levels in the mesolimbic dopamine system/VTA [38,43]. This deteriorated dopamine function may be related to the intense craving associated with withdrawal in human drug addicts [4]. Taken together, initial or incidental drug use may enhance dopamine output and increase the resulting feelings of pleasure. Over time, however, this physiological reward function may collapse, causing dopamine concentrations to drop down and possibly leading to depression and other negative affective states.

Various addictive drugs share the common feature of stimulating the same dopaminergic brain reward system (for example, heroin enhances dopamine levels by increasing dopamine release, whereas cocaine inhibits the dopamine reuptake), and this action has been related to their appetitive motivational effects [4,6,64]. Thus, appetitive rather than aversive motivation may induce drug-taking behavior and addiction [37]. Reward processes, based on dopaminergic signaling, clearly exhibit a positive motivational potential and with that they may be useful for medical strategies focusing on behavior change, i.e., stress management and lifestyle modification programs (see below). In fact, reward mechanisms are implicated in placebo phenomena and CAM therapies, as well as in settings that place emphasis on wellness and feelings of well-being [8,14,26,27,53]. However, individuals who actively 'use' their reward circuits for behavioral or motivational reasons are in constant danger of losing control over their behaviors (i.e., motivational toxicity).

VTA neurons communicate with the nucleus accumbens by dispatching dopamine from the terminals of their long projections to receptors on nucleus accumbens neurons [15,16]. This dopamine pathway from VTA to nucleus accumbens appears to be a critical component of the reward physiology, including pleasure and addiction: in animals with lesions in these regions, a loss of interest in drug consumption has been observed [6,52]. Moreover, cocaine and other stimulants temporarily disable the return of dopamine to the VTA neuron terminals and opiates, in addition, bind to inhibitory neurons in the VTA that usually shut-down the dopamine production (thereby allowing dopamine-secreting cells to release dopamine). Both strategies finally support excess dopamine to act on the nucleus accumbens [15,16]. Opiates may further generate a strong 'reward message' by acting directly on the nucleus accumbens [6,59]. Again, we find the complexity that rules dopaminergic reward processes.

Other monoamines (as well as acetylcholine, endorphins etc.) may also participate in these processes [8,14,65]. With regard to neuroanatomy, particular attention may be paid to dopaminergic neurons of the ventral tegmentum that project to the nucleus accumbens, amygdala, prefrontal cortex and other forebrain structures (as described above). Other regions like the hippocampus and additional limbic areas may also be of interest. All these parts of the brain's reward circuitry seem to communicate back and forth with VTA and nucleus accumbens, thereby frequently involving glutamate signaling [6]. When drugs of abuse increase dopamine release from the VTA into the nucleus accumbens, they further alter the responsiveness to glutamate [6,15,16]. Changes in sensitivity to glutamate may then enhance both the release of dopamine from the VTA and responsiveness to dopamine in the nucleus accumbens, thereby promoting CREB and delta FosB activity (see above). Furthermore, it seems that this altered glutamate sensitivity strengthens the neuronal pathways that link memories of drug consumption and related cues with high reward, thus feeding the desire to seek the drug, i.e., vicious circle [15,16,52]. Finally, drugs of abuse obviously influence the shuttling of glutamate receptors in the reward pathway [6].

Taken together, pleasure phenomena critically involve dopaminergic signaling. This dopamine-associated reward physiology may also play a role in the placebo effect and related mechanisms. It may therefore be useful in various health care settings and medical procedures. Placebos may even be helpful in long-term substitution programs for the treatment of drug addiction, since they are able to induce dopamine release in the brain – which is a key element of drug addiction as well [53]. However, endorphins and other signaling molecules have to be taken into consideration too. Pleasure and addiction may exhibit common pathways: Substances of abuse – such as nicotine – may increase CNS dopamine levels, thereby improving mood and affect (or compensating for chronically lowered dopamine concentrations as seen, for example, in several affective disorders) [10,63]. This potentially pleasure-inducing capacity of drug consumption may be accompanied by the development of drug dependence. Thus, the neurochemical mechanisms and physiologi-

cal consequences underlying pleasure and addiction are complex and ambiguous.

Belief, cognition and social support

It has been suggested that the placebo effect is basically mediated by dopaminergic – and possibly morphinergic – reward mechanisms and that this placebo-related reward physiology is associated with positive therapy expectations, i.e., expected clinical benefits [14,53]. Hence, placebo effects may involve anticipatory pleasure and positive motivation. The placebo response relies on trust and belief, and this connection has its neurobiological roots predominantly in limbic and frontal/prefrontal brain activity [53,66,67,68]. Furthermore, pleasure is a subjective quality of experiences that involve reward circuitry stimulation and a specific pattern of CNS activity, including dopamine signaling (see above). Studies on the neurobiological processes underlying pleasure, reward and addiction have focused on limbic, frontal and prefrontal CNS activity [14,24]. However, brainstem and basal ganglia (e.g., striatum and pallidum) may also be important [23,24,69]. Lesions in the ventral pallidum, for example, can impair normal sensory pleasure [23]. The basal ganglia are normally in control of inhibitory GABAergic and dopaminergic neurons that seem to communicate with the reward system [23,69]. Thus, the brain's reward and motivation circuits include different CNS regions that may serve various separate functions but overlap in their reward signaling pathways. Almost all of these structures and mechanisms obviously exhibit some form of an association with cognitive functions, trust or belief [8,14,24]. With regard to addiction, which represents a possible dangerous outcome of pleasure-seeking behavior, these regions are also involved in more complex cognitive and motivational functions, such as the ability to track, update and modulate the salience of a reinforcer as a function of context or expectation and the ability to control or inhibit prepotent responses and behavior [24].

Belief has an emotional component in that the brain's motivation and reward circuitry – linked to limbic system and emotional memory – will be reinforced with a positive emotional valence attached to the believed in person, idea, or thing [8,14]. This emotionalized memory, potentially accompanied by 'somatic markers' (e.g., pleasant bodily sensations that may escort an emotion), sets the 'feeling tone', i.e., it strongly influences what 'feels right' to a person [8]. Furthermore, pleasure and emotion may reinforce a belief and trigger positive physiological reactions even against rationality [70]. Thus, belief in a doctor or therapy may stimulate naturally occurring health processes [14]. These subjective 'self-healing' processes may particularly involve limbic structures (i.e., 'remembered wellness'), and they may be based on endogenous signaling molecules like morphine [8,14,27]. Taken together, the subjective modulation of incoming information in the brain – e.g., following prior stimulation of the sensory organs – may be an important factor in pleasure and placebo phenomena likewise. This may particularly be true when positive qualities or experiences like pleasant sensations, touch, attention, feelings of well-being or protection are involved [14].

Pleasurable experiences are effectively capable of improving concentration and cognitive function, e.g., memory [14,26,71]. This may be due to hippocampal/limbic activation, including reward circuitry stimulation [8]. Again, positive emotions – linked to rewarding stimuli – may reinforce this process. Clearly, pleasurable experiences and feelings are interconnected, and the emotion it imparts can be viewed as a process of reinforcing a positive belief so that rational thought can not hinder the strength of the belief [72]. Thus, pleasure is a powerful tool to elicit an emotional response (i.e., limbic activation) and fulfil expectations without the use of rational information processing [14]. Social interaction, for example, can be a source of such pleasant feelings and sensations. The possible pleasure of touch, attention, closeness or protectedness as well as sexual stimulation or communication – all these activities and conditions may improve cognitive, motivational or emotional functions, and they may even effectively reduce stress [26,73–75]. Thus, pleasure may reinforce trust and belief, thereby improving cognition, well-being and health. Social support may facilitate this process, which potentially is also inducible by placebo or CAM therapies [14,26,76,77].

Health implications

We have learned that pleasure, in general, can be healthy experience. Now we want to take a closer look at this obvious association between pleasure and health. Procedures that particularly focus on the healthy aspects of pleasant activities – and that could therefore serve medicine and health care [1,14,26] – may consist of classical medical treatments, complementary approaches or psychological interventions, i.e., 'positive psychology'. Thereby, positive psychology is putting emphasis primarily on the existence of health-promoting and -protecting factors in each individual, that is, salutogenic or resistance resources [2,26,76–80]. These resources like personality hardiness, exercise, social support, sense of coherence etc. may enhance feelings of comprehensibility, manageability, meaningfulness, control, closeness and commitment in life and in stressful situations [76,77,79]. Besides effectively reducing stress, the fact that life is principally seen as a challenge and a positive – that is, enjoyable, rewarding or pleasurable – event may itself shape well-being and health [76–78,80]. People with high salutogenic qualities believe in their strengths, expect the positive and find meaning in almost everything they encounter [73–75]. Further, these salutogenic factors generally serve a positive and productive motivation and may scare away feelings of depression or helplessness, even when a realistic (and possibly overwhelming) threat occurred [76,78,80]. They may not always prevail. Salutogenic resources and pleasur-

able experiences, however, can facilitate an optimistic and 'humorous' attitude towards life (see below).

The field of positive psychology is about valued subjective experiences: pleasure, well-being, contentment or satisfaction in the past, hope and optimism for the future and flow or happiness in the present [81]. At the individual level, it is about positive individual traits (such as the capacity for love and vocation, courage, interpersonal skill, aesthetic sensibility, perseverance, forgiveness, originality, future mindedness, spirituality, talent and wisdom), and at the group level, it is about civic virtues and conditions that promote responsibility, nurturance, altruism, civility, moderation, tolerance and work ethic [81]. Researchers in the field of preventive medicine have discovered that these traits and factors represent human strengths that buffer against stress and illness [2,26,76–81]. Optimism, the ability to enjoy pleasurable events, honesty, faith or the capacity for flow and insight may also be named here [12,81]. Today's medicine has learned the importance of fostering these attitudes and virtues for preventive reasons [1]. Practitioners need to accept that much of the valuable work they do is to generally amplify strengths rather than repair broken parts [81]. Hence, the new paradigm has brought the science and usefulness of pleasure, reward, human strengths and resilience to light. Individuals are now seen as decision makers with choices, preferences and the possibility of becoming masterful and efficacious – or, in adverse circumstances, help- and hopeless [82,83]. A suitable side effect of positive psychology, however, may be that normal people grow stronger and get more productive [81].

What is the difference between being optimistic or enjoying pleasurable experiences on one hand and being realistic on the other? Is it possible to be both, optimistic and realistic, at the same time? Indeed, researchers in the field of positive psychology suggest that someone can still be happy or aspire to an overall optimistic attitude while confronting life realistically – and working productively to improve health or the conditions of existence [81]. In fact, pleasure may be the key feature that keeps 'positive minded' people doing so. We have learned, however, that these people could also acquire an elevated risk of becoming addicted to pleasurable activities and stimulants (see above).

Mihaly Csikszentmihalyi has observed increased quality of life when work and leisure engage one's skills. Between the anxiety of being overwhelmed or stressed and the apathy of being underwhelmed or bored lies a zone in which people experience *flow* [84,85]. This mind-state appears to be extremely pleasurable and productive, since people are kept in the moment, absorbed by their current activities, showing a beneficial physiology – and just feeling well [12,14,26,84,86]. Thereby, the state of flow resembles the relaxation response described earlier, possibly involving brain's reward pathways and limbic activity [12,14,26]. However, human beings can be proactive and engaged or, alternatively, passive and alienated, largely depending on the social conditions in which they develop and function [87]. Accordingly, positive psychology research focuses on factors that promote natural processes of self-motivation and healthy psychological development [87]. Conditions are thus under examination that facilitate intrinsic motivation, self-regulation and well-being. Hence, joy and pleasure can be interpreted as such potentially self-applicable factors, providing internal (versus external) control and self-esteem. Moreover, the innate needs of happiness, competence, autonomy and relatedness – when satisfied – may yield enhanced self-motivation and health [14,87].

Motivation concerns aspects of activation or intention. Consequently, it lies at the core of biological, cognitive and social regulation [87]. Motivation is highly valued in health care, because it produces behavioral changes or adjustments and can mobilize others to act [87]. When motivation occurs in conjunction with optimism, its health-supporting abilities could even be stronger. Furthermore, psychological beliefs such as optimism, personal control and a sense of meaning are well-known for their health-protecting capacities [61,88]. It seems now that optimism may facilitate health and prevention even when 'unrealistically optimistic' beliefs about the future – i.e., positive illusions (delusions?) – are involved [88]. The ability to find meaning in the present experience may also be associated with a less rapid course of illnesses [88]. Taken together, psychological beliefs such as meaning, control and optimism act as salutogenic factors, regardless of the 'appropriateness' of their occurrence. Positive illusions (or maybe even denial) on one hand or a fighting spirit on the other – when people generally stay optimistic and full of hope, thinking they'll overcome a threat and enjoying pleasurable experiences that still exist for them, they potentially display better health parameters and outcomes compared to pessimistic people [84,87,88]. Additionally, motivation, joy and optimism may characterize individuals high in resistance resources and quality of life. The ability to enjoy pleasurable experiences – and thereby activate brain's reward and motivation pathways – may serve health and can thus be recommended even in life threatening situations [14,26,88].

Complementary medical treatments and approaches can elicit pleasurable experiences or sensations [14]. Clearly, CAM possesses health-promoting capacities [14,26]. CAM may, in addition, induce feelings of flow, relaxation and well-being, thereby probably involving the CNS reward circuitry [8,12,14,26,27]. Optimism, belief and motivation play a critical role in CAM therapy [8,14]. Hence, pleasurable CAM effects resemble the placebo response – with particular reference to the non-specific parts of the CAM physiology [14]. However, pleasure holds beneficial and detrimental abilities likewise (as described). It may trigger flexibility, positive motivation, optimism or healthy behaviors and yet still has addiction and motivational toxicity on its template. This can be a question of dose: moderately pleasant experiences, particularly when mediated via

regular stimulation of the sensory organs, may be helpful for the induction of behavior change (e.g., lifestyle modification or stress management programs), since it involves positive or appetitive motivation, potentially facilitating biologically beneficial motivational behavior (see above). However, the pleasurable aspect of CAM can also be found, counter intuitively, in more stressful and competitive situations, such as the work environment. Gratification (i.e., reward) is a stress buffer and possible source of health, pleasure and happiness. Gratification in association with work (money, esteem, job security, career chances) leads to comparable positive results, that is, it elicits the same beneficial response [61,81,89]. In terms of neurobiology, work-related gratification potentially relies on the same uniform stimulation of CNS reward pathways already illustrated. Therefore, regardless of the original source of gratification, experiencing pleasure or engaging in joyful activities can activate areas in the brain responsible for emotion, attention, motivation and memory (i.e., limbic structures), and it may further serve to control the autonomic nervous system [27,90,91]. This specific CNS activity pattern appears to exert protective effects, even on the brain itself [14,26]. Moreover, anxiolytic effects of pleasurable experiences may occur by promotion of an inhibitory (GABAergic) tone in specific areas of the brain [92]. In this regard, methionine enkephalin signaling brings with it antibiotic activity (see Figure 1). Thus, pleasure clearly is capable of stimulating health, well-being and productivity.

Pleasure seems to possess a coordinating influence on a network of cortical and subcortical limbic and paralimbic structures, regions that are intimately involved in the regulation of cognition, emotion and autonomic, endocrine or vegetative functions [14]. Modulation of this neuronal network could initiate a sequence of effects by which pleasurable activities regulate multisystem functions [14]. Meditation – given as an example for a CAM technique that potentially induces pleasurable sensations and feelings of well-being (thereby involving the relaxation response) [26] – has been shown to increase left-sided anterior activation of the brain, a pattern that is associated with positive affect [93]. Again, positive emotion-related brain activity is a substantial part of the CNS reward circuitry, and the frontal regions of the brain not only are involved in relaxation response pathways, but clearly exhibit a specialization for the processing of emotions as well [11]. Davidson et al. recently suggested that left-sided anterior activation is associated with more adaptive responding to negative and/or stressful events [93,94]. Specifically, individuals with greater left-sided anterior activation have been found to show faster recovery after negative provocation [94]. The two brain hemispheres may thus not act symmetrically in pleasure phenomena, underlining the complexity of the reward and motivation physiology. For example, when teenagers listen to pleasurable music of their choice, parts of the frontal and temporal lobe in the left hemisphere get activated [95,96]. In contrast, when they listen to music they obviously dislike, the same areas on the other side (i.e., right brain) are active. Further, deeper CNS structures get involved: pleasurable music not only stimulates the temporal and frontal (left-anterior) brain, but also activates parts of the limbic system like the cingulate gyrus [95]. Dissonant or unpleasant music, however, activates right parahippocampus and amygdala (related to fear and anxiety). As described above, dopamine, GABA, glutamate and other neurochemicals such as serotonin and endorphins (and even the stress hormones) may be important for this particular brain activity pattern found in pleasant/unpleasant experiences. Interestingly, in people listening to their preferred music they exhibited lower blood pressures accompanied by changes in peripheral opiate signaling [97,98]. This finding may actually mirror changes in chemical messenger functions in the brain, i.e., limbic via morphine [99,100,101].

Taken together, pleasurable experiences can be a source of health protection and promotion, but still carry the risk of addiction and other negative outcomes within. This potential for addiction may be directly related to endogenous morphine signaling. Moreover, the underlying physiology is complex and has to be studied further.

Discussion

Pleasure clearly is an important neurobiological phenomenon. Research usually sees pleasure as an enjoyable experience, i.e., a feeling that results from joyful activities (as described). However, pleasure is much more complex and we should take a closer look. Some researchers think that it might be helpful to distinguish positive experiences that are pleasurable from those that are enjoyable [81]. Following this discussion, pleasure can be seen as the good feeling that comes from satisfying homeostatic needs such as hunger, sex and bodily comfort, whereas enjoyment may refer to the good feelings people experience when they break through the limits of homeostasis – when they do something that stretches them beyond their current existence [81]. Hence, enjoyment rather than pleasure may lead to personal growth and development, yet providing good feelings or long-term happiness, i.e., 'fun' [81]. However, this is a speculative aspect and it's still imaginable that, with reference to neurobiology or underlying molecular mechanisms, both phenomena are identical. Interestingly, when given a chance, most people choose pleasure instead of enjoyment, that is, they choose to watch television over reading a challenging book, even when they know that their usual hedonic state during television is mild dysphoria, whereas the book can, for example, produce flow [81]. Thus, pleasure or pleasant experiences (or enjoyment) not only serve entertainment, but can also alter motivation, behavior and personal growth.

The brain's reward and motivation circuitry with its limbic components represents the crucial neurobiological system underlying pleasure phenomena. It not

only serves pleasure and motivation, but also involves aspects of behavior, reproduction and sexual activity, emotion, belief and trust, memory, cognition, stress physiology and autonomic functions, relaxation and well-being – to name a few [8,10,14,26,96]. The reward physiology is complex. Thereby, the limbic system in general seems to play an important role, but some specific CNS regions involved in the pleasure physiology have also been identified. As described above, the VTA and nucleus accumbens, together with amygdala (i.e., extended amygdala) and other frontal/prefrontal or mesolimbic structures like the medial forebrain bundle can be mentioned here. Neurotransmitters potentially acting on these structures are, for example, dopamine, GABA, glutamate, serotonin, acetylcholine, morphine, nitric oxide, noradrenaline, cortisol as well as endocannabinoids.

Complementary medical procedures can induce pleasure. Sensations that accompany CAM therapy (e.g., via direct stimulation of the sensory organs) may activate limbic or other areas of the brain related to the reward and motivation circuitry. Secondary physiological changes and bodily reactions may follow, i.e., autoregulatory mind/body reactions [14]. Music, for example, can produce happiness, since it also influences limbic and reward pathways responsible for feelings of pleasure and happiness [12]. Pleasant music can thus stimulate the same CNS reward and motivation processes that get involved in eating, drinking, sex or drug consumption, thereby reducing anxiety and depression [12,14,86]. Music therapy, seen as an example for a common CAM-associated intervention, can be a healthy – or healing – experience [86]. However, we realize how potentially close pleasure and addiction are bound together. The question is: What is the crucial difference between good or bad (i.e., ameliorating or detrimental) pleasure phenomena and outcomes of pleasurable activities?

Much of behavior can be explained by simple processes of approaching pleasant and avoiding painful stimuli [102]. Normally, appetitive motivation relies on physiological reward processes that are capable of governing normal behavior and are most often associated with goals that have benefited the species (or the organism) from an evolutionary biology perspective [4]. This can't be bad. However, we have to distinguish normal from abnormal behavior and artificial from natural rewards. Also, we must examine the type of influence on the CNS pathways that rewarding stimulants exert and the dose/quantity of a pleasant experience or activity.

Natural rewards can be modulated by the activity of the brain's reward and motivation circuitry. Feeding, sexual activity or maternal behavior can be facilitated each by opiate activation of the reward system [25,49,59]. The origin of the VTA (i.e., ventral tegmental dopamine system) seems to provide an important neurochemical interface where exogenous opiates and endogenous opioid peptides can activate a CNS mechanism involved in appetitive motivation and reward [4,14]. Obviously, endogenous morphinergic signaling may also play a role [4]. This is especially true since endogenous morphine biosynthesis may involve elements of dopamine metabolism [103,104], linking two critical signaling systems. Additionally, endogenous morphine has been found in hippocampal tissues [99,100] and morphinergic signaling has been demonstrated to release constitutive nitric oxide here [101], linking morphine to limbic structures and nitric oxide effects. Thus, the VTA serves as a appetitive motivation system for diverse behaviors, since it controls both normal and pathological behaviors [4,14,20,42]. However, artificial rewards and drugs – in contrast to natural stimuli that work, for example, by moderate sensory organ stimulation – are capable of acting directly on VTA and nucleus accumbens pathways, allowing only little flexibility and modulation to interfere (see above). Consequently, artificial rewards can diminish self-control and beneficial motivational behavior, leading to a potentially dangerous or detrimental outcome, i.e., motivational toxicity [4]. They may therefore be considered biologically senseless. Nonetheless, artificial and natural rewards can not always be differentiated easily. The difference, however, could be a question of dose.

One can imagine that the effects of strongly and directly rewarding substances that are ingested in high concentrations and immediately induce 'pleasure' are different from moderate but still pleasant experiences that do not reach comparable concentrations or show a more pulsatile physiology. Natural rewards may not boost such a flood of neurochemicals and stimulating signaling molecules or they may not completely surpass normal physiology. However, the distinction can also be made by the build-up of appetence: natural rewards, i.e., pleasurable experiences like eating or sex, usually depend on a preceding build-up of appetence (e.g., hunger) to fully develop their pleasure potential [17,69,105]. Following the pleasurable experience, appetence decreases and then needs a certain time span to newly reach its former levels and intensity. During this time, the same 'appetizing' experience can even induce aversion [17]. Addictive drugs, in contrast, immediately build up high appetence levels that are not released completely or only for a short time after drug consumption [15,16,52]. This frustrating fact produces even more appetence: one can not stop the pleasure-seeking activity that now starts to take control over normal behaviors (i.e., motivational toxicity). Without experiencing a break, a restless vicious circle has been initiated, forcing to seek for the one and only motivational goal and anticipated relief (see above). Flexibility, variability, biological complexity and personal growth or freedoms have been sold for addiction. Taken together, natural rewarding activities and artificial chemical rewarding stimuli act at the same locations, but while natural activities are controlled by feedback mechanisms that activate aversive centers (i.e., aversive motivation), no such restrictions bind the responses to artificial stimuli [4,65]. Moreover, reward substrates that directly act on the brain's reward pathways are more potent than other rewards, such as

food or water: subjects prefer to choose self-imposed starvation when forced to make a choice between obtaining food and water or direct electrical stimulation of the reward circuitry [106]. However, another distinguishing feature between normal pleasure and addiction, as described, is the lack of satiation. These two features (super-potent reward and lack of satiation) are important characteristics of direct activation of the CNS reward pathways [4]. We can assume that nature has not made preparation, that is, has not planned for this artificial short-cut to occur.

The hypothesized activation of the ventral tegmental reward system by endogenous opioid peptides or opiates can offer an explanation of seemingly paradoxical behavior: the voluntary self-infliction of stress or pain [4,8,14]. Events normally considered stressful and thus aversive may activate the CNS reward system through the release of chemical messengers, i.e., morphine, induced by the stressor [4,8,14,27]. This could explain the attraction some individuals display to seemingly aversive stimulation (e.g., risk-taking behavior or self-infliction of painful stimuli). In some situations, the appetitive motivational effect of these behaviors may override the normal aversive effect that usually induces withdrawal behavior [4]. Consequently, in certain conditions, approach behavior indicative of appetitive motivation may be produced by an aversive stimulus normally avoided. This is most likely perhaps in situations where the effects of the stress-associated endorphin release out-last the abrupt termination of the painful or aversive stimulus [4]. Also, cognitive processes could label the stressor as non-threatening, thus permitting the pleasurable effects to dominate affective tone. Finally, the aspect of challenge involved in risk-taking behaviors, for instance, could represent the 'enjoyment' component related to rewarding activities (as described earlier), possibly leading to personal growth and development. Taken together, avoidance and approach are connected with stress physiology and 'pleasure response', thereby potentially including stress-associated endorphin signaling.

Music has been shown to possess the ability to decrease stress hormone levels in stressful (challenging) situations and alter endogenous plasma opiate alkaloid levels, eventually facilitating relaxation and feelings of well-being [12,107,72,98]. Hence, pleasant music can be used as an effective calming and stress-reducing intervention, therefore involving limbic pathways, i.e., autonomic-emotional integration system [12,72,86]. Moreover, nitric oxide and opiate autoregulatory signaling have been demonstrated or discussed in association with further CAM therapies (e.g., acupuncture, relaxation response techniques, massage therapy) [8,14,26,27,108–114]. These molecules that possess a strong CNS affinity and are capable of reducing stress may also be involved in the placebo or pleasure response, promoting positive CAM effects [2,14,26,27,53,66,67,113–124]. Recent information suggests that morphinergic signaling is a part of this hypothesis. Endogenous morphine has been found in various neural tissues as well as in limbic structures [14,57,125–133,104]. Morphine has been found in hippocampus [99,132,100] and when added to rat hippocampus stimulates nitric oxide release, demonstrating a mu3-like effect [101]. The opiate mu receptor subtype, designated mu3, has been cloned, is opiate alkaloid selective and opioid peptide insensitive [134], strongly supporting the hypothesis of an endogenous morphinergic signaling system. Additionally, these reports demonstrate the presence of morphine precursors in various mammalian tissues, including brain. The psychiatric implications of this system have been examined as well, including brain reward circuitry [14,121]. Thus, morphine, given its reported effects and those exerted via stimulation of constitutive nitric oxide release, may form the foundation of the common signaling in CAM and pleasure phenomena. Indeed, morphine may additionally represent signaling that allows one to make rationale short cuts, since being rationale, from time to time, can be too time consuming – i.e., emotional appetitive motivation [135].

Belief and expectation are, by nature, important ingredients of the placebo response. Placebo effects, however, may involve morphinergic signaling [14,136,137]. Neurons immunoreactive for morphine are largely present all along the extension of the periaqueductal grey matter, in brainstem raphe nuclei and cortex [14,127], implicating morphinergic neural pathways in the placebo response. Additionally, the prefrontal cortex (particularly the dorsolateral aspect) has been shown to be involved in the representation of cognitive control, goal determination and expectation – and thus plays a crucial role in the placebo response as well [14,136]. Moreover, the prefrontal cortex possesses close neural connections to limbic components, such as the hippocampal formation and cingulate cortex, where morphine immunoreactivity is largely present in neurons and fibres [14,131]. These areas play a major role in memory, motivation as well as in pleasure or reward processes (see above). Furthermore, endogenous morphine appears to modulate memory – thereby, for example, weakening the memory of a nociceptive or aversive experience [138]. Taken together, limbic areas are connected to the frontal/prefrontal cortex, which integrates emotion, memory, belief, expectation, motivation and reward processing, i.e., affective and motivational responses [8,139]. Also, prefrontal mechanisms may trigger opiate release in the midbrain [136]. Thus, the endogenous opiate aspect of pleasure phenomena seems to be crucial but needs more attention and thorough research to be conducted. This may be of particular importance for health implications in association with pleasurable experiences, since these can promote flexibility and self-control, possibly decreasing motivational toxicity (as seen in drug addiction), hence serving as a therapeutic tool. However, the duration and dose of pleasure or reward – that is, reward circuitry stimulation – appears to be they key element of interest.

Conclusions

Pleasure can serve health, but is also capable of promoting addiction and other dangerous outcomes or behaviors (i.e., motivational toxicity). It is a complex neurobiological phenomenon, relying on reward circuitry activity and limbic processes. These CNS processes can involve dopaminergic signaling. Moreover, opioid peptides and endogenous morphinergic mechanisms play a role as well. Natural rewarding or pleasurable activities are necessary for survival and appetitive motivation, usually governing beneficial biological behaviors like eating, sex and reproduction. Thus, pleasure is much needed. However, artificial stimulants (e.g., addictive drugs) or 'too much' of a pleasurable activity may not be as beneficial, since flexibility and natural control of behaviors may be deteriorated. Clearly, addiction includes a loss of control over normal behaviors and appetitive motivational goals. Addictive drugs, in addition, are capable of directly and strongly acting on reward pathways, thereby influencing motivation physiology.

Moderate pleasurable experiences, nonetheless, are able to enhance biological flexibility, complexity and health protection. Thus, pleasure can be a resistance resource, or it may serve salutogenesis and prevention. Natural rewards are regularly mediated by sensory organ stimulation, thereby exhibiting a potential association with complementary medical approaches. The existence of subjective CNS phenomena like feelings of pleasure, joy and happiness and their commonalities with CAM mechanisms may emphasize the significance of naturally occurring health processes and general self-care capabilities. Trust and belief may be part of this self-healing potential. Further, the placebo response physiologically resembles pleasure phenomena, since both involve the brain's reward and motivation circuitry stimulation and subjective feelings of well-being. Again, morphinergic autoregulatory signaling may be involved.

Pleasure facilitates limbic thrust of belief and trust into the body's equation for restoring or maintaining health. Thereby, pleasure promotes a healthy state of dynamic balance. In humans, cognition and belief (e.g., in love and trust) are vital for reward and pleasure experiences. Social contacts, in addition, provide pleasure, hence survival. These functions of pleasurable experiences may even stimulate personal growth and development. Furthermore, they can serve to induce healthy behavioral changes and lifestyle modifications, including stress reduction or stress management programs. However, there is a lot more of research to be done to better understand the nature, neurobiology and maybe dangerous side of pleasure. Also, the involvement of endogenous morphinergic processes has to be studied further. When this has been done, however, one can imagine pleasurable activities, enjoyment and CAM to become part of future therapeutic strategies in regular medicine.

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