The Endogenous Opioid Neurotransmission and Seasonal Affective Disorders

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Abstract

The intricate link between physiology and seasonal mood changes remains elusive, whereas brain neurotransmitter signaling seems to stand at the central stage. It is recently disclosed that the endogenous opioid signaling demonstrates seasonal patterns, as is predominant in the brain socio-emotional circuits and also, peripherally in tissues crucial for energy homeostasis. Compared to other types of neurotransmissions, such as the serotonin signaling, brain opioid signaling is thought to have a top-tier role in sociality. Further, the endogenous opioid is a neuropeptide with large molecular mass. In contrast to the faster response of small

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molecular neurotransmitter signaling, the neuropeptide signaling is characterized with slower response and more sustained effects, favoring a potential role in the low speed of seasonal mood changes. In the current chapter, potential roles of central and peripheral opioid receptor signaling, as well as relevant body-brain interactions, inducing seasonal affective disorders are discussed.

Keywords

Mu-opioid receptor signaling · Opioid · Neurotransmission · Neuropeptide · Seasonal affective disorders · Seasonality · Daylength · Photoperiod · Positron emission tomography · Neuroimaging · Brain · BAT-brain axis · Body-brain interaction

Abbreviations

BAT	Brown adipose tissue
MOR	Mu-opioid receptor
PET	Positron emission tomography
SADs	Seasonal affective disorders

Introduction

When dark seasons are approaching, our brain and body adjust their functions accordingly. For instance, the brain mu-opioid receptor levels decline (Sun et al. 2021), possibly a sign for lazy and volatile mood and vulnerability to stressors. Brown adipose tissue activity, a crucial player in energy homeostasis, is enhanced in the meanwhile (Wiesinger et al. 1989; Au-Yong et al. 2009; Sun et al. 2023a), which may further affect hormone regulation and brain functions and modulate the desire for diet via the functional BAT-brain axis (Sun et al. 2023b; Sun and Nuutila 2024; Laurila et al. 2021; Li et al. 2018). Bodily response to seasons is a complex process with integrated physiological changes including patterned brain physiological changes and body-brain interactions. Imbalanced adaption to seasons may lead to aberrant central and peripheral physiological functions associative to seasonal depression.

Seasonal Affective Disorders and Neurotransmitter Signaling

Subjective experience of seasonal mood changes can range from the extreme and pathological end of the spectrum, namely, seasonal affective disorders (SADs), through the mildly pathological, known as subsyndromes of SADs, to a normal seasonal rhythm. SADs are characterized by recurrent depressive episodes that occur at specific times of the year, especially during dark seasons. Key symposiums of SADs include persistent feelings of sadness, fatigue, insomnia, anxiety, and changed appetite with increased craving for carbohydrates (Rosenthal et al. 1984). Numerous reviews of the diagnosis, epidemiology, symptoms, and clinical interventions of

SADs are available in the literature (Magnusson and Partonen 2005; Wehr and Rosenthal 1989; Eastwood and Peter 1988; Westrin and Lam 2007; Melrose 2015).

Prevalence of SADs or subsyndromes is often found to be higher in regions with higher latitude (Rosen et al. 1990), and bright light therapy is the first-choice clinical intervention for SADs (Terman et al. 1989). It has been reported that 85% of normal Finns notice seasonal variations in own mood and behavior (Grimaldi et al. 2009), and the presence of SADs or its subsyndromes in Finland is up to 39% (Saarijarvi et al. 1999). This phenomenon may be partly explained by geographical location with a large natural span of daylength, Fig. 1.

Mounting evidence suggests that the onset of SADs in dark seasons is associated with seasonal changes of major types of neurotransmitter signaling, as reviewed previously (Magnusson and Boivin 2003; Levitan 2007; Praschak-Rieder and Willeit 2012). For instance, dark seasons are associated with reduced postsynaptic serotonin receptor availability in the normal population (Matheson et al. 2015; Spindelegger et al. 2012). Failed downregulation of serotonin transporter levels is often thought to elicit SADs (Mc Mahon et al. 2018; Mc Mahon et al. 2016). In the meanwhile, brain imaging data in subjects with no clinical symptoms of SADs show increased of striatal dopamine synthesis in fall and winter (Eisenberg et al. 2010; Kaasinen et al. 2012). Dopamine transporter binding, in contrast, is found lower in the brain regions such as the left caudate during dark seasons (Booij et al. 2023), as is further linked with onset of SADs (Neumeister et al. 2001). A recent study by the author also indicates that the striatal dopamine D2/D3 receptors levels are elevated during dark seasons in the healthy population (Sun et al. 2024). Therefore, while seasonal rhythms in neurotransmitter signaling are part of the neuroplasticity toward the dynamics of the climate, they also contribute to the development SADs when these rhythms become dysregulated.

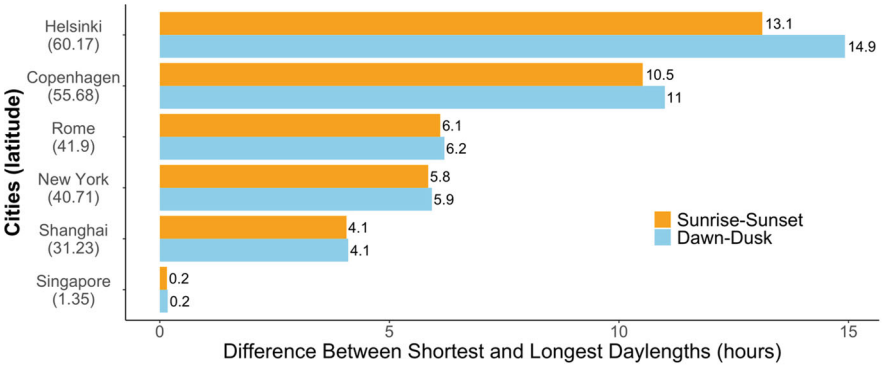

Fig. 1 Difference between longest and shortest daylength in selected cities of the northern hemisphere. Daylength is calculated as the interval either between sunrise and sunset (orange color), or between dawn and dusk (blue color, with civil twilight considered). The impact of civil twilight turns to be larger in regions with higher latitude

The Central Mu-Opioid Receptor Signaling and Function

Within the biochemical frameworks of the human body, there exists a complex system dedicated to modulating pain, reward, and numerous other physiological processes. This system, known as the endogenous opioid system, orchestrates its effects through a family of neurotransmitters and receptors strategically dispersed throughout the central and peripheral nervous systems. The endogenous opioids function through multiple types of opioid receptors, classically involving the *mu*, *delta*, *kappa*, and nociceptive opioid receptors; the family of opioid receptors continues to grow with atypical opioid receptors being discovered (Che and Roth 2023).

Key characteristics of the mu-opioid receptors (MORs) are summarized in Table 1 and also systematically reviewed previously (Che and Roth 2023; Valentino and Volkow 2018; Pasternak and Pan 2013). One well-known function of MOR signaling is to modulate the perception of pain. When activated by endogenous opioids (e.g., endorphins) or exogenous opioids (e.g., morphine), these receptors can block or reduce the transmission of pain signals in the central nervous system. In the meanwhile, this receptor function is crucial for trait-level social behavior (MacHin and Dunbar 2011), and mice with genetic knockout of MOR show autistic-like syndrome (Becker et al. 2014). Especially, endogenous opioid signaling seems to have top-tier effect over other neurotransmitters in modulating the brain social domain function (Panksepp et al. 1980b).

Beyond that, recent neuroimaging studies also highlight its crucial roles in brain acute response to social cues, showing increased MOR signaling leads to reduced brain BOLD level responses to socio-emotional stimuli including vocal binding and distress signals (Sun et al. 2022) and arousing and painful scenes (Karjalainen et al. 2017; Karjalainen et al. 2019). Therefore, the MOR signaling is important for both trait-level sociality and healthy brain social and affective functions.

Table 1 Basic properties of the MOR signaling

Properties	Details
Type of receptor	G protein-coupled receptors (GPCRs)
Subtypes	Primarily MOR; variants suggested by alternative splicing
Discovery	Discovered in the 1970s through radioligand binding studies
Primary functions	Pain modulation, reward, mood regulation, respiratory and gastrointestinal functions
Location	CNS, PNS, the gastrointestinal tract, BAT
Endogenous ligands	Endorphins (particularly beta-endorphin)
Signal transductions	Inhibition of adenylate cyclase, modulation of ion channels, MAP kinase pathway activation
Physiological effects	Analgesia, euphoria, respiratory depression, constipation, hormone regulation, immune modulation
Roles in disease	Opioid addiction, pain disorders, potential role in mood disorders
Drug development	Focus on analgesics with reduced side effects, treatments for addiction, treatment for obesity

Seasonal Patterns of Brain MOR Signaling

PET imaging is the sole method in providing quantitative measurement of neuroreceptor signaling in a cognitive brain (Henriksen and Frode 2008). Using specific radioactive tracers, PET allows for mapping the distribution of targeted molecules, for example, the [^{11}C]carfentanil PET imaging of in vivo MOR availability. Based on a historical database brain PET images at the Finnish national PET Centre, the author studied and reported, for the first time, the seasonal pattern of MOR signaling in healthy humans (Sun et al. 2021). In brief, central MOR receptor density, or technically referred as receptor availability for specific binding, demonstrates an inverted-U functional relationship with local daylength. This pattern of variation is found in brain regions spanning the socio-emotional brain circuit, underscoring a physiological underpinning of seasonal patterns of brain social functions, Fig. 2. Accordingly, the dark winter and mid-summer are characterized with low level of MOR signaling in the brain, while spring and fall seasons hold the peaks of MOR signaling.

This result is further supported by parallel findings in an animal model study (Sun et al. 2021). Specifically, experimental rats are kept under a condition simulating the local seasonal cycles of daylength, while other environmental factors are kept consistent; repeated [^{11}C]carfentanil PET imaging (three to four times per rat) are conducted in between. MOR receptor availabilities in brain regions including the neocortex, striatum, and thalamus are analyzed. In line with findings based on the human database, a similar inverted-U relationship between photoperiod and brain regional MOR availability is disclosed. This evidence, via maintaining unchanged

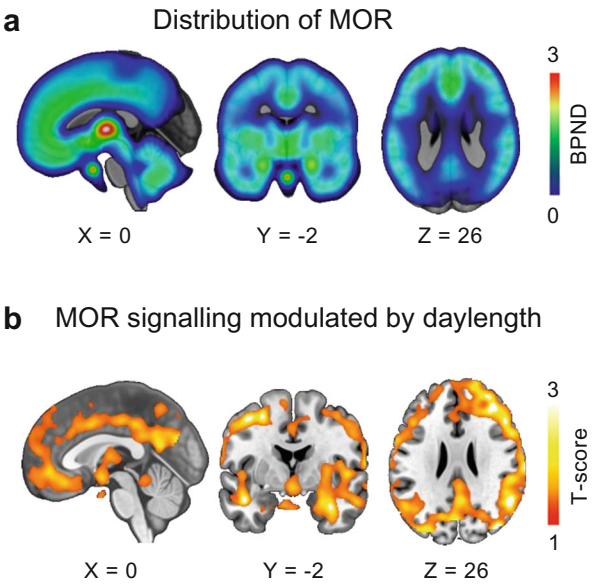

Fig. 2 Human brain mu-opioid receptor (MOR) signaling is sensitive to photoperiod. PET images showing the distribution of MORs (i.e., specific binding of radiotracer [^{11}C]carfentanil to the receptor) in the healthy brain (**a**), and statistical mapping showing regions where the MOR availability is sensitive to the variation of daylength (**b**). (The figure is adapted from (Sun et al. 2021) under the Creative Commons CC BY license)

for other environment factors including temperature and humidity, as well as for diets, establishes a causal link between photoperiod and brain MOR signaling.

Brain MOR Density and Mental Health

The complex relationship between the plasticity of MOR signaling and mental health remains unsettled. Lower MOR availability in healthy individual may be an indicator of increased likelihood of psychiatric conditions (Nummenmaa et al. 2020), as well as elevated acute brain responses to emotional social cues (Sun et al. 2022). To that end, higher brain MOR availability may deliver a sedative effect toward emotional stimulation, prohibiting the vulnerability to emotional disturbances. On the other hand, early life stress, associated with higher level of anxiety and depression, predicts higher chance of opioid misuse, which suggests altered MOR signaling (Oswald et al. 2021). Opioid drugs are frequent substances identified in intentional overdose deaths (Miller et al. 2020), and its intentional overdose deaths demonstrate a seasonal pattern with the peak found in Spring-Summer time in the United States (Han et al. 2022); interestingly, this aligns with a natural peak of MOR availability in healthy populations (Sun et al. 2021). Postmortem studies have also established that suicide victims have increased MOR densities (Gross-Isseroff et al. 1990; Gabilondo et al. 1995). Thus, the elevated brain MOR density from the norm may be associated with increased tendency for opioid drug misuse and depression with suicide attempts.

The complicated, apparently controversy, models related to brain MOR density and mental health may be partly derived from the limitations of the methodology in quantifying MOR density in the brain. In those methods, the basal opioid concentrations are either assumed for a normal/low level (e.g., a baseline PET quantification), or simply impossible to sort out (e.g., in the postmortem measures). Increased MOR density in psychiatric populations as found in postmortem studies, indicating a pathological augmentation of MOR signaling, may actually indicate a feedback mechanism to battle the low efficiency of opioid signaling of the patients. However, this remains unsettled. Therefore, when the holistic picture of the MOR signaling (Che and Roth 2023; Al-Hasani and Bruchas 2011) are not available and upstream and downstream ends of the singaling pathway are unknown, cautions need to be taken in interpreting the findings.

Seasonal Patterns of MOR Signaling in BAT

In contrast to the established roles of brain MOR signaling in social behavior and brain affective functions, peripheral MOR function is typically recognized in conveying the local analgesic effect of opioid peptides (Stein et al. 1993). In addition, MOR signaling may be involved in cellular immune responses and inflammation, since evidence shows that tissue injury augments peripheral opioid analgesia with an increase of MOR expression (Hassan et al. 1993; Stein et al. 2001; Zhou et al. 1998). In mammals, MORs are found to be expressed in muscles, intestine, adrenal, kidney, lung, liver,

stomach, and BAT (Grider and Makhlouf 1991; Wittert et al. 1996; Sun et al. 2023a). Function of the peripheral MOR signaling may be part of the sympathetic innervation, for instance, in controlling BAT thermogenesis (Cao and Morrison 2005).

A recent study of the author reports the expression of MOR in BAT in rats (Sun et al. 2023a), Fig. 3, and further demonstrates a linear relationship between photoperiod and BAT MOR availability, showing that shorter photoperiod is associated with higher amount of available MORs. The elevated MOR singling during dark seasons goes in line with evidence showing that BAT has higher activity during winter seasons (McElroy and Wade 1986; Au-Yong et al. 2009). Elevated MOR signaling and the parallel increase of BAT thermogenesis in dark seasons may suggest an important role of MOR signaling in BAT metabolism. Further, the somewhat inverse seasonal patterns of MOR availability in the brain and BAT (Fig. 4) may suggest a season-dependent BAT-brain communication, crucial in modulating feeding behavior (Sun et al. 2023b).

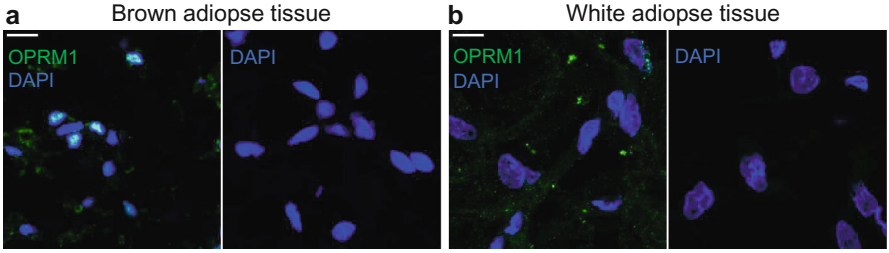

Fig. 3 Mu-opioid receptors (MORs) are expressed in the brown adipose tissue (BAT). Immunofluorescence images by anti-MOR antibody (OPMR1, green) confocal microscopy. Images demonstrate expression of MOR in (**a**) brown adipose tissue and (**b**) white adipose tissue. Nuclei are counterstained with 4′,6-diamidino-2-phenylindole (blue, left panel), and omission of the anti-MOR antibody resulted in no green staining. Scale bar = 10 μm. (The figure is adapted from (Sun et al. 2023a) under the Creative Commons CC BY license)

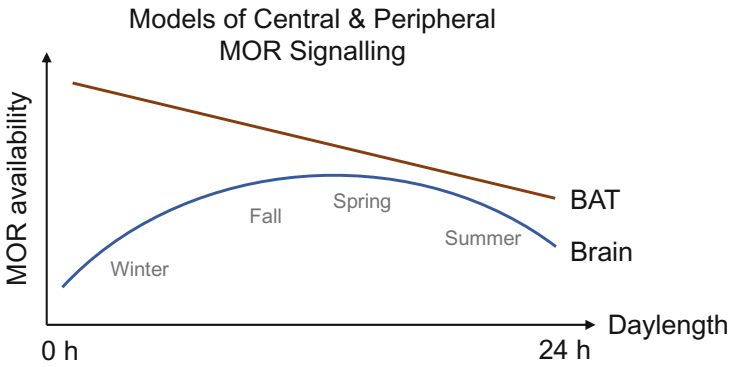

Fig. 4 Seasonal patterns of mu-opioid receptor (MOR) signaling in the brain and the brown adipose tissue (BAT) under Finnish geographic conditions

Potential linkage between MOR signaling to BAT metabolism may be explained by the opioid-induced inflammatory responses (Mercadante et al. 2019). In dark seasons, increased MOR availability in BAT as quantified by PET may also be partly contributed by the reduced amount of plasma opioid, since the peripheral secretion of opioid ligands bear great seasonal fluctuation with substantially lower levels in winter (Lincoln and Baker 1995). To note, PET measures of receptor availability is typically thought to index receptor density, since the basal extracellular level of neurotransmitters is generally low (Maidment et al. 1989). However, due to accelerated photoperiodic cycles, impact of basal opioid concentrations on PET outcomes cannot be simply neglected (Sun et al. 2023a). In the meanwhile, winter-stimulated growth of BAT is associated with reduced inflammation, which is an indicator for lowered plasma opioid (McElroy and Wade 1986; Hassan et al. 1993; Stein et al. 2001; Zhou et al. 1998; Villarroya et al. 2018). Therefore, increased MOR signaling and BAT activity in dark seasons may be both due to reduced amount of plasma opioids. Despite of the unsettledness of this suspect, seasonal variation of MOR signaling in the BAT suggests a system level interaction between MOR signaling and glucose metabolism, calling for in-depth studies.

The Functional Gut-BAT-Brain Axis and SADs

The sophisticated interaction between the gut, BAT, and the brain plays a pivotal role in maintaining energy homeostasis that usually follows the seasonal rhythms. Also, increasing evidence demonstrates the crucial roles of this functional gut-BAT-brain axis in modulating brain functions, so as to affect the feeding behavior. For instance, the secretin hormone, primarily secreted by the S cells in the duodenum, is recently found to modulate the BAT activity and, via this functional axis, modulate brain functions associative to satiation in both rodents and humans (Laurila et al. 2021; Sun et al. 2023b; Li et al. 2018). While one central symptom of SADs pertains to changed appetite with increased energy update in dark seasons, whether this functional gut-BAT-brain axis plays substantial roles in the onset of SADs remains to be disclosed. Most notably, the gut is a resource of key neurotransmitters, such as the serotonin with crucial roles in mood and emotions. The studies of the author (Sun et al. 2023a; Sun et al. 2021) may also disclose a MOR-mediated mechanism that further enlarges our knowledge on the role of this functional BAT-grain axis in triggering SADs via neurotransmission, energy homeostasis, and the inflammatory pathways.

Neuropeptide Signaling

Another outstanding feature of the MOR signaling pathway is related to its biochemical nature, Table 2. Compared to the fast-acting small-molecular neurotransmitter signaling, action of neuropeptides is on a larger scale of seconds, minutes, or hours (Van Den Pol 2012). Endogenous opioid such as the beta-endorphin has

Table 2 Basic characteristics of small molecular neurotransmitter and neuropeptide signaling pathways

Aspects	Small molecular neurotransmitter signaling	Neuropeptide signaling
Sizes	Small molecules (<1000 Daltons)	Large peptides (>1000 Daltons)
Synthesis	Synthesized in the cytoplasm and packaged into synaptic vesicles	Synthesized in the cell body and transported to terminals via axonal transport
Release	Released via exocytosis upon depolarization of the presynaptic neuron	Release via exocytosis or regulated secretion
Diffusion	Fast diffusion and rapid degradation; reuptake by adjacent cells	Slower diffusion and prolonged effects due to larger size and slower degradation
Receptors	Activate postsynaptic receptors on adjacent neurons or effector cells	Bind to specific receptors on postsynaptic neurons or on distant target cells
Signal duration	Fast-acting, short-lived effects (milliseconds to seconds)	Slower onset and longer-lasting effects (seconds to hours)
Role in regulation	Mood, anxiety, reward processing, motor control, attention, cognition	Mood, stress responses, anxiety, reward processing, feeding behavior, social behavior
Examples	Acetylcholine, dopamine, serotonin, glutamate	Oxytocin, vasopressin, substance P, endorphins

molecular weights tens of times of smaller neurotransmitters such as dopamine, Fig. 5. Also, specific characteristics of neuropeptide signaling include its release with no restriction to synaptic specializations, the diffusion for a longer distance known as volume transmission (Fuxe et al. 2005), and posttranslational processing (Gomes et al. 2020). Besides, the neuropeptide signaling are highly integrated in the process of metabolism and reproduction (Crown et al. 2007). These special characteristics further propose an important role of MOR signaling in SADs.

Future Prospective

Despite that evidence shows the impact of photoperiod on in vivo MOR signaling, many questions and concerns remain. For example, does sunlight exposure causally affect the seasonal variation of brain opioid signaling in humans? It is well known that activated opioid signaling delivers sedative effect to pain and to anxiety (Panksepp et al. 1980a). Compared to other types of neurotransmissions (e.g., serotonin signaling), the opioid signaling pathway has a top-tier role in social comfort (Panksepp et al. 1980b), and it plays a central role in sociality of primates (MacHin and Dunbar 2011). With brain PET imaging, it is found that routine social behavior activates endogenous opioid signaling (Manninen et al. 2017; Nummenmaa et al. 2016). Therefore, the tie between sociality and endogenous opioid signaling seems to be solid. Social behavior, on the other hand, is largely affected by day-to-day weather changes, including sunlight exposure. It is therefore possible that the linkage between daylength and

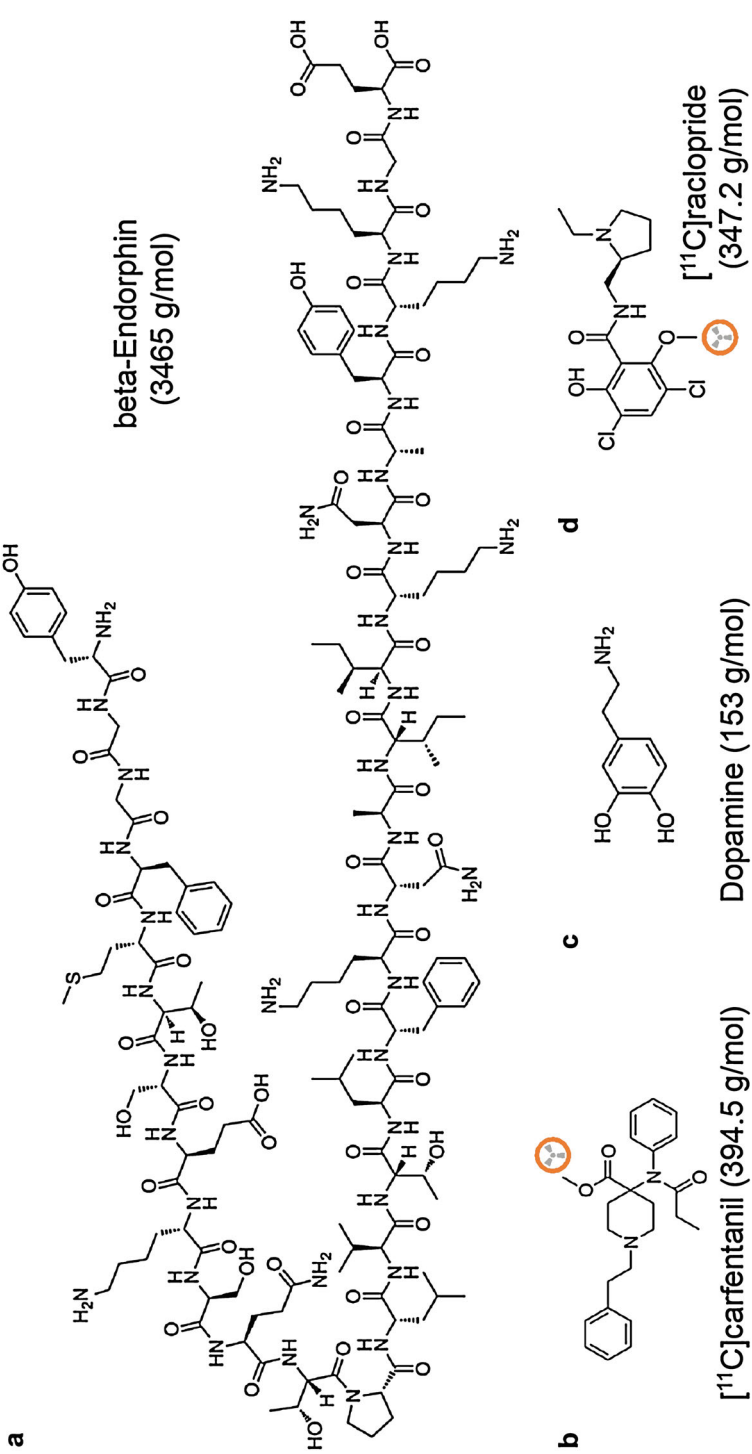

Fig. 5 Molecular structures and weight of beta-endorphin (**a**) and the radiolabeled [^{11}C]carfentanil for in vivo PET measures (**b**), dopamine (**c**), and the radiolabeled [^{11}C]raclopride for PET measures (**d**)

social activities is further and perfectly geared with a communication between patterned social behavior and brain opioid signaling. While seasonal patterns of neurotransmissions have been better studied for endogenous serotonin signaling (Praschak-Rieder et al. 2008; Kalbitzer et al. 2010) and the dopamine signaling (Booij et al. 2023; Kaasinen et al. 2012; Sun et al. 2024), for the opioid signaling, related evidence is still limited (Sun et al. 2023a; Sun et al. 2021). Further, despite that the rat neuroimaging study suggests a causal relationship between daylight and the opioid signaling, behaviors of the rats are not measured in the study (Sun et al. 2021). Based on the current evidence, therefore, caution needs to be taken for concluding that sunlight is the driver for the disclosed seasonal patterns of brain opioid signaling. Simply, the intimate connections between daily weather, social behavior, and endogenous opioid signaling make this examination rather complicated.

On the other hand, peripheral MOR signaling is greatly under-investigated, which also involves the MOR-mediated body-brain interactions. Based on the preliminary evidence showing that daylight turns peripheral MOR signaling in tissues crucial for energy homeostasis and brain function, peripheral opioid signaling may bear great value in shaping neuroplasticity toward environmental challenges. In addition, seasonal cycles of general hormone levels (Tendler et al. 2021) and its impact on body-brain interaction and cognition (Sun and Nuutila 2024) have not been investigated systematically.

Taken together, future studies should focus on the intimidate linkage between light exposure and endogenous opioid signaling beyond the confounding social factors. This may include evidence at cellular and tissue levels, as well as system-level repeated measures with the social traits well controlled for. Also, great effort is required to tag into the basic principles underlying peripheral opioid signaling and body-brain physiological interactions in the context of the seasonal cycles.

Applications to Other Scenarios

This chapter reviewed current findings on the potential role of endogenous mu-opioid signaling pathway in SADs. Findings also provide supportive evidence on photoperiodicity in human physiology and brain functions. The historic debate on photoperiodicity in humans has been evolving (Bronson 2004), reflected by massive neuroscientific evidences (Meyer et al. 2016; Sun et al. 2021; Cho et al. 2015; Chastin et al. 2019; Mooldijk et al. 2022; Golder and Macy 2011; Sun et al. 2016). Researchers who argue against the strict application of photoperiodicity assert that the traditional understanding of photoperiodicity may not fully capture the nuanced interactions between light exposure and human biology in diverse settings. Moreover, they highlight the need for a more contextual and personalized approach, acknowledging that individuals may differ in their sensitivity to light and its impact on circadian rhythms. In contrary, researchers supporting the concept of photoperiodicity in humans emphasize the evolutionary significance of our biological clocks and the fundamental role that natural light plays in regulating various physiological processes. Proponents of photoperiodicity contend that disruptions

to this natural cycle, particularly through increased exposure to artificial light and screens at inappropriate times, can lead to a range of health issues (Cho et al. 2015; Mooldijk et al. 2022; Meyer et al. 2016; Golder and Macy 2011). Daylength has large span in regions near the polar areas, and in those regions, the prevalence of seasonal affective disorder is high. The seasonal patterns of the MOR signaling pathway in the general population may be highly linked with social behavior and brain affective functions that are shaped by seasons. Intriguingly, instead of individualized sunlight exposure hours, findings that natural daylength being associated with the endogenous MOR signaling highlight the robustness of photoperiodicity in the human physiology and brain functions. Understanding and respecting the inherent connection between neurotransmitter signaling and the natural light-dark cycle may be essential for promoting optimal health and well-being. Also, understanding the seasonal patterns of endogenous opioid signaling may help predict seasonal bursts of opioid drug abuses and inspire related clinical interventions.

Mini-dictionary of Terms

- **Brown adipose tissue**. It is a specialized type of adipose (fat) tissue known for a higher density of mitochondria and thermogenesis. In humans, it was traditionally thought to be present only in infants. However, recent research in recent years has shown that brown adipose tissue also exists in significant amounts in adults, albeit typically in smaller quantities and different locations compared to infants.
- **Civil twilight**. It begins in the morning when the center of the sun is 6 degrees below the horizon and ends at sunrise. In the evening, civil twilight starts at sunset and ends when the center of the sun reaches 6 degrees below the horizon.
- **Daylength**. Daily sunlight hours that are calculated as interval between sunrise and sunset. It may also be calculated as interval between dawn and dusk by considering the civil twilight.
- **Neuropeptide signaling**. It refers to the process by which neuropeptides, which are small protein-like molecules, transmit signals within the nervous system. It plays a crucial role in regulating pain perception, stress responses, mood regulation, appetite control, and social behavior.
- **Neurotransmission**. A process by which nerve cells communicate with each other or with other cells in the body. It involves the transmission of chemical signals (e.g., dopamine, serotonin, and beta-endorphin) known as the neurotransmitters.
- **Positron emission tomography**. A medical imaging technique relying on radioactive tracers labelled with positron-emitting radionuclide. Multiple types of radioactive tracers have been developed to target biochemical processes such as neurotransmission and metabolism.
- **Seasonal affective disorders**. A subtype of depression characterized by recurrent episodes of depressive symptoms that coincide with particular seasons, mostly during fall and winter with short daylight hours.

- **Volume transmission**. A concept used in neuroscience to describe a mode of signaling where neurotransmitters diffuse through the extracellular fluid, affecting multiple neurons or other cells over a relatively wide area rather than acting solely at synaptic junctions.

Key Facts

Key Facts of Endogenous Opioid Signaling

Endogenous opioids are neuropeptides with much larger molecular mass compared to small molecular neurotransmitters like dopamine.
Classic types of opioid receptors include the mu (μ), delta (δ), and kappa (κ) nociceptive opioid receptors, with new receptors continue to be discovered.
Opioid receptors are found in various regions of the central nervous system and peripheral tissues.
Endogenous opioid signaling is involved in the regulation of mood and sociality, pain perception, reward, stress, and inflammatory responses.
Drugs that target the opioid system are widely used in clinical practice for pain management, anesthesia, and the treatment of opioid addiction.
Mu opioid receptor signaling and its related drug abuse demonstrate seasonal patterns.

Key Facts of Seasonal Affective Disorders

- Seasonal affective disorder is a type of depression that occurs at a specific time of year, typically when sunlight hours are shorter.
- Key symposiums include persistent feelings of sadness, fatigue, insomnia, anxiety, and increased craving for carbohydrates.
- It is more common in high-latitude regions with significant seasonal changes in sunlight hours.
- Light therapy is a first-choice treatment approach for the disorder.
- The cause of the disorder remains elusive, with evidence showing that changes in light exposure affect the body's circadian rhythm and neurotransmitter signaling.

Summary Points

- The intricate link between physiology and seasonal mood is greatly underinvestigated.
- Mu-opioid receptor signaling in the socio-emotional brain circuit shows seasonal patterns.
- Brown adipose tissue mu-opioid receptor signaling shows seasonal patterns.

- Body-brain interactions via neurotransmitter signaling may contribute to the seasonal affective changes.
- Neuropeptide signaling bears specific properties for a potential role in seasonal affective changes.

Competing Interest Declaration The author(s) has no competing interests to declare that are relevant to the content of this manuscript.

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