Universidade Federal do Rio de Janeiro

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SÍNDROME DA APNÉIA OBSTRUTIVA DO SONO E PREJUÍZO COGNITIVO EM PACIENTES COM DEPRESSÃO

RIO DE JANEIRO

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Disertação de mestrado submetida ao Corpo Docente do Programa de Pós-Graduação em Psiquiatria e Saúde Mental – PROPSAM do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Mestre em Psiquiatria.

Orientador: SÉRGIO EDUARDO DE CARVALHO MACHADO

Co-orientador: ERIC SIMÓN MURILLO-RODRIGUEZ

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RESUMO

A depressão é um dos transtornos psiquiátricos mais comuns, apresentando prevalência de aproximadamente 16% da população em alguma fase da vida. É atualmente a quarta causa de incapacidade no mundo, com importante queda na produtividade no trabalho e significante prejuízo no convívio social. Quando se trata da relação entre depressão, cognição e sono, muitas dúvidas surgem. Seriam os déficits cognitivos uma consequência da depressão? Seria o humor depressivo decorrente da perda de determinadas funções cognitivas? Seriam os transtornos de sono, e mais precisamente a síndrome da apnéia obstrutiva do sono (SAOS), um fator de piora do perfil cognitivo desses pacientes? Poderia o tratamento da apnéia modificar o desfecho do tratamento antidepressivo? Embora vários estudos tenham sido realizados até o momento com o objetivo de esclarecer a relação entre a SAOS e a depressão, o mecanismo fisiopatológico exato desta inter-relação ainda é pouco conhecido. A hipótese avaliada neste estudo é de que a alta probabilidade de SAOS impactaria diretamente no desempenho cognitivo dos pacientes com depressão. Foi verificado o efeito do alto risco de SAOS na gravidade dos sintomas depressivos, no grau de sonolência diurna e no comprometimento da atenção, memória de trabalho e velocidade de processamento. Nesta dissertação são apresentados 2 estudos que exploram essa relação e os possíveis mecanismos fisiopatológicos para a mesma.No estudo 1 foi observado que a alta probabilidade de SAOS, em pacientes depressivos, aumentou o grau de sonolência diurna, a intensidade dos sintomas da depressão e piorou o perfil cognitivo dos mesmos. No estudo 2 foi realizada uma revisão da literatura existente sobre a relação da hipocretinacom os transtornos psiquiátricos, sendo demonstrado que seus receptores e a distribuição dos mesmos apresentam papel fundamental nessa relação, que ainda precisa ser melhor compreendida. A partir dos achados encontrados nesta dissertação, torna-se possível traçar uma relação entre a SAOS e depressão, principalmente no que se refere aos sintomas cognitivos, fisiológicos e sociais de ambas as patologias.

Palavras-chave: Depressão, déficit cognitivo, síndrome da apnéia obstrutiva do sono, sonolência diurna, hipocretina

ABSTRACT

Depression is among the most common psychiatric disorders and its lifetime prevalence is approximately 16%. It is the fourth cause of disability worldwide, with low working capacity and significant social impairment. When we try to understand the relationship between depression, cognition and sleep, many questions emerges. Is the cognitive impairment a consequence of depression? Could be depressive mood a consequence of cognitive impairment? Can sleep disorders, especially obstructive sleep apnea syndrome (OSAS), make the cognitive function worse in depressive subjects? Could be the treatment for OSAS correlated with a better outcome in these subjects? A lot of research have been make trying to understand the relationship between OSAS and depression, but the exact mechanism how this relationship works is still unknown. Therefore, the hypothesis evaluated in this study was that the high risk of OSAS, in patients with depression, worsen their depressive symptoms, daytime sleepiness and cognitive functions. More specifically, will be verified the effect of the high risk of OSAS on the symptoms of depression, daytime sleepiness, attention, working memory and processing speed. In this paper, we present 2 studies that evaluates this relationship and the mechanisms that could explain it. In the first study, it wasobserved that higher risk of OSAS, in depressive patients, would be correlated with higher degree of daytime sleepiness, depression symptoms and cognitive impairments. The second study was a review of the existent literature about the relationship between hypocretin and psychiatric disorders and it1s possible that its receptors and anatomical distribution of them have a role on this relationsheep. Based on the data found in this research it is possible delineate the relationship between OSAS and depression, particularly with respect to cognitive, physiologic and social symptoms shared by these two disorders.

Key-words: Depression, cognitive impairment, obstructive sleep apnea syndrome, daytime sleepiness, hypocretin

LISTA DE SIGLAS

AA	Alternating Attention
ACTH	Adrenocorticotropic Hormone
APOE	Apoliproteína E
AVC	Acidente Vascular Cerebral
BDI-II	Beck Depression Inventory
BNST	Nucleus of the Dorsal Striatum
BPA	Bateria Psicológica para Avaliação da Atenção/Psychological Battery for Attention
BQSA	Questionário de Berlim para Apnéia do Sono/Berlin Questionnaire Sleep Apnea
CPAP	Dispositivo de Pressão Positiva Contínua em vias aéreas
CRH	Hormônio Liberador de Corticotrofina/Corticotrophin Releasing Hormone
CSF	Cerebrospinal Fluid
DA	Divided Attention
DORAS	Antagonistas Duais/Dual Orexin Receptors Antagonists
EDS	Excessive Daytime Sleepiness
ESE	Escala de Sonolência de Epworth
ESS	Epworth Sleepiness Scale
GABA	Ácido Gama-Aminobutírico
HHA	Eixo Hipotálamo-Hipófise-Adrenal
HLA	Antígeno Leucocitário Humano/Human Leukocyte Antigen
HOSAS	Higher Risk of OSAS
HPA	Hypothalamic-Pituitary-Adrenal Axis
IAH	Índice de Apnéia e Hipopnéia
IL-1	Interleucina-1
IL-16	Interleucina-16/Interleukin-16
LOSAS	Lower Risk of OSAS
MINI	Mini-entrevista Psiquiátrica Internacional/Mini International Neuropsychiatric Interview
MINI-MENTAL	Mini-exame do Estado Mental
MRI	Magnetic Ressonance Imaging
MSLT	Multiple Sleep Latency Test

OSAS	Obstructive Sleep Apnea Syndrome
OXR1	Receptor de Orexina-1
OXR2	Receptor de Orexina-2
PET	Tomografia Computadorizada por Emissão de Pósitrons
PSG	Polissonografia/Polysomnography
PVN	Núcleo Talâmico Paraventricular/Paraventricular Thalamic Nucleus
PVT	Teste de Vigilância Psicomotora
REM	Movimentos Rápidos dos Olhos/Rapid Eye Movement
RNM	Ressonância Nuclear Magnética
SA	Sustained Attention
SAOS	Síndrome da Apnéia Obstrutiva do Sono
SED	Sonolência Excessiva Diurna
SOL	Sono de Ondas Lentas
SORAS	Antagonistas Únicos/Single Orexin Receptors Antagonists
SPI	Índice de Velocidade de Processamento/Speed Processing Index
SPECT	Cintilografia de Perfusão Cerebral
TLMS	Teste das Latências Múltiplas do Sono
TNF	Fator de Necrose Tumoral/Tumor Necrosis Factor
TTS	Tempo Total de Sono
WMI	Índice de Memória Operacional/Working Memory Index

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1 INTRODUÇÃO

A depressão é uma das doenças psiquiátricas mais comunse sua prevalência é de aproximadamente 3 a 16% da população geral (FLECK et al, 2009; KESSLER et al, 2005; WARAICH et al, 2004). É atualmente a quarta causa de incapacidade no mundo, com importante queda na produtividade laborativa e prejuízo social (TRIVEDI et al, 2014; BROMET et al, 2011; FLECK et al, 2009; KESSLER et al, 2005*)*.É um transtorno que está associado a altos índices de morbimortalidade, sendo o custo para a saúde pública muito alto, devido a eficácia limitada e ao longo tempo de tratamento com os antidepressivos convencionais (LAGROTTE et al, 2016; SOLÉ et al, 2015; LEPINE et al, 2011; KESSLER et al, 2003; STEWART et al, 2003; SCHULZ et al, 2002). Sua relação com déficits cognitivos já é conhecida, porém o debate sobre quais domínios da cognição são afetados permanece.

1.1 DEPRESSÃO E DÉFICITS COGNITIVOS

Embora a metanálise realizada por Rock e colaboradores em 2013 tenha evidenciado que a função executiva, memória e atenção sejam os domínios cognitivos mais afetados na depressão, outros autores concluem que há uma ampla variedade nasfunções acometidas, não havendo um padrão específico de déficit (BAUNE et al, 2018; COTRENA et al, 2016; PEHRSON et al, 2015; ROCK et al, 2013; BEBLO et al, 2011; HUANG, 2009). De acordo com uma metanálise recente, o tamanho de efeito dessa associação pode variar de *d*=0.32-0.97 para diferentes funções executivas (SNYDER, 2012). Alterações nos componentes executivos como controle da atenção, flexibilidade cognitiva, controle inibitório e fluência verbal são achados comuns em pacientes depressivos, e têm sido atribuídos a alterações em áreas frontolímbicas como o córtex pré-frontal dorsolateral e ventromedial, e o giro frontal superior (COTRENA et al, 2016; NITSCHKE et al, 2004). A circuitaria neuronal envolvida na cognição e depressão é criada pela interação dos neurônios serotoninérgicos, noradrenérgicos e dopaminérgicos, e a conexão entre córtex cerebral, tálamo e gânglios da base. Os circuitos cognitivos muitas vezes se sobrepõem aqueles envolvidos no humor e nas emoções, e recebem influência do eixo hipotálamo-hipófise-adrenal (HHA) e amígdala, ambos associados aos transtornos de humor (TRIVEDI et al,2014). Evidências recentes sugerem que alterações nas regiões cerebrais envolvidas com a cognição podem ocorrer em pacientes com múltiplos

episódios depressivos ou naqueles com mais de 2 anos de doença. Grande parte dos pacientes, inclusive os considerados “bons respondedores”, apresentarão sintomas residuais, sendo o déficit cognitivo o mais comum deles (SOLÉ et al, 2015). É importante ressaltar que a presença desses sintomas residuais aumenta o risco de recorrência da depressão e ainda que a grande maioria dos pacientes não correlacionam seu déficit cognitivo à depressão (BAUNE et al, 2018). Em média, 20% dos pacientes em remissão relatam dificuldades com concentração e tomada de decisões (CONRADI et al, 2011; NIEREMBERG et al, 2010).

Muitas perguntas ainda existem com relação a expressão do déficit cognitivo nesses pacientes, como a duração dos sintomas, a implicação desses sintomas no desfecho do paciente e a relação dos antidepressivos com a cognição (TRIVEDI et al, 2014). O papel da serotonina na regulação da flexibilidade cognitiva, impulsividade e atenção já é bem conhecida, e estudos mais recentes tem demonstrado que algumas citocinas e neuromoduladores também possuem uma função na cognição (TRIVEDI et al, 2014; PUING and GULLEDGE, 2011). Embora com tantas pesquisas, a natureza da disfunção executiva associada com a depressão permanece desconhecida (BREDEMEIR et al, 2016). Existem algumas evidências de que os sintomas cognitivos melhoram com o uso dos antidepressivos e resultados preliminares mostram que algumas classes podem ser mais efetivas que outras na melhora desses sintomas (TRIVEDI et al, 2014; HUANG, 2009). Alguns autores sugerem que o déficit na memória de trabalho ocorra devido a alterações persistentes na atenção seletiva e tem sido correlacionada com anormalidades persistentes no córtex pré-frontal (HUANG, 2009; BLUMBERG, 2003; TRICHARD, 1995). Quanto ao índice de velocidade de processamento, alguns autores defendem a teoria de que este índice se encontra alongado ou atrasado devido a alterações temporárias na atenção, memória, função visuo-espacial e tempo de reação (BULBENA et al, 1993), no entanto, um estudo recente sugeriu que a depressão poupa o estágio de estímulo do processamento e afeta o estágio motor do mesmo (KALB et al, 2006; BONIN-GUILLAUME et al, 2004).

Uma forma de avaliar o déficit cognitivo na depressão é fazendo referência ao conceito de cognição fria e quente, proposta por Sahakian e colaboradores (ROISER et al, 2013). A proposta é separar os diferentes componentes da cognição em relação as emoções, de maneira que a cognição fria (emoção independente) se refere a funções como atenção, função executiva, memória e velocidade de processamento,

funções estas que não são modificadas pelo estado de humor do paciente, enquanto a cognição quente (emoção dependente) descreve processos que são susceptíveis a modulação dependente do estado de humor, como atenção, memória de trabalho e testes de percepção (BAUNE et al, 2018). As funções executivas “frias” estão relacionadas a regiões pré-frontais dorsolaterais, enquanto as "quentes" são mediadas pelo córtex órbito-frontal, corpo estriado ventral e sistema límbico (CHAN et al, 2008; VOLKOW& BALER, 2014). Embora o processamento emocional e a cognição social estejam no centro das atenções da depressão, sua importância funcional tem sido pouco valorizada. Entendendo-se que esses aspectos da cognição (quente, fria e social) parecem estar intimamente correlacionadas com a função psicossocial, fica claro que toda a dimensão da cognição na depressão estende-se além do nível fenomenológico e possa representar um elemento crucial no curso da doença.

1.2 SÍNDROME DA APNÉIA OBSTRUTIVA DO SONO E DEPRESSÃO

A síndrome da apnéia obstrutiva do sono (SAOS) é uma doença caracterizada por episódios de redução ou ausência total de fluxo respiratório, devido a uma obstrução, não necessariamente mecânica, das vias aéreas superiores. É de longe a patologia do sono mais comum, afetando em média 2% das mulheres e 4% dos homens e estando associada a altos índices de morbidade e mortalidade, além de diminuição da qualidade de vida (NARDONE et al, 2016; GARVEY et al, 2015; BEST et al, 2013; DAABIS & GHARRAF, 2013; MANNARINO et al, 2012; MACEY et al, 2010; HARRIS et al, 2009; GRUNSTEIN et al, 2008). Estima-se que 80% dos homens e 93% das mulheres com SAOS moderada e grave não tenham diagnóstico, uma vez que o quadro clinico muitas vezes é pobre em sintomas, principalmente nos quadros mais leves (KERNER & ROOSE, 2016; BEST et al, 2013; LEE et al, 2008). Esses eventos respiratórios levam a uma fragmentação crônica do sono, com consequente redução do sono de ondas lentas (SOL) e de sono de movimentos rápidos dos olhos (REM), e ainda geram episódios de dessaturações com hipoxia intermitente, o que leva a sonolência excessiva diurna (SED), alterações no humor, déficit cognitivo, síndrome metabólica, fadiga, dentre outros (GAGNON et al, 2014).Vários estudos têm investigado a relação da SAOS com a depressão, mas essa relação ainda é pouco compreendida, embora a prevalência de depressão em pacientes com SAOS seja relativamente alta (KERNER& ROOSE, 2016; LAGROTTE et al, 2016; WHEATON et

al, 2012; EJAZ et al, 2011; NAIR et al, 2011; EL-SHEIKH et al, 2010; HARRIS et al, 2009; PEPPARD et al, 2006; OHAYON, 2003; FILE, 1992). Daabis e Gharraf, por exemplo, encontraram uma prevalência de sintomas depressivos de 51% em homens apneicos e as taxas de sintomas depressivos são mais altas em pacientes com SAOS sem tratamento do que na população geral (DAABIS & GHARRAF, 2012; WAHNER-ROEDLER et al, 2007; MILMAN et al, 1989; MOSKO et al, 1989). Alguns autores ainda demonstram que em média 20% dos indivíduos depressivos apresentam algum distúrbio respiratório do sono não-diagnosticado, principalmente SAOS (SHARAFKHANEH et al, 2005; OHAYON, 2003). Um estudo publicado em 2015 que incluiu 224 pacientes com 70 anos ou mais, com SAOS grave (índice de apnéia-hipopnéia IAH>30), encontrou uma taxa de 23,2% de depressão (MARTINEZ-GARCIA et al, 2015). Essa alta prevalência de sintomas depressivos na SAOS pode ser explicada por vários mecanismos. Os dois mecanismos mais aceitos são a fragmentação do sono e a hipóxia intermitente (DAABIS & GHARRAF, 2012). A fragmentação do sono é a causa primária da SED nesses pacientes, levando a sintomas depressivos. Vários estudos demonstram uma relação direta entre a alta pontuação na escala de sonolência de Epworth (ESE) e a presença de sintomas depressivos (DAABIS & GHARRAF, 2012; KJELSBERG et al, 2005; YUE et al, 2003; SFORZA et al, 2002).Já foi amplamente observado que a SAOS está associada a uma elevação nos níveis de inteleucina 16 (IL-16) e do fator de necrose tumoral (TNF), citocinas que atuam como mediadores da SED, além disso a depressão está associada com uma resposta imunológica envolvendo citocinas pró-inflamatórias, entre elas interleucina 1 (IL-1), IL-16 e TNF (AL-HAKEIM et al, 2015; HARRIS et al, 2009; IRWIN & MILER, 2007; VGONTZAS et al, 2000; VGONTZAS et al, 1997). Quanto à hipóxia, alguns dados recentes sugerem que esta possa estar associada a alterações no metabolismo da substância branca, o que impactaria diretamente nos sintomas depressivos (GAGNON et al, 2014; FIRBANK et al, 2004; ALOIA et al, 2004; TAYLOR et al, 2003). Estudos recentes utilizando tensor de difusão demonstram alterações na substancia branca de várias regiões cerebrais que poderiam estar relacionadas ao transtorno de humor, como lobos frontal, temporal e sistema límbico (KUMAR et al, 2012; MACEY et al, 2008). Além disso, muitos dos sintomas diurnos apresentados pelos pacientes apneicosse assemelham aos sintomas depressivos, dificultando o diagnóstico e o tratamento de ambas as patologias (DAABIS & GHARRAF, 2012).

1.3 SÍNDROME DA APNEIA OBSTRUTIVA DO SONO E DÉFICIT COGNITIVO

O déficit cognitivo é um dos sintomas diurnos da SAOS e geralmente é caracterizado pelo déficit na atenção, memória episódica, memória de trabalho e nas funções executivas, embora com funções de linguagem preservadas (GAGNON et al, 2014; BUCKS et al, 2013; HOTH et al, 2013; TULEK et al, 2013; ALCHANATIS et al, 2008; ALVAREZ & EMORY, 2006; ALOIA et al, 2004; BARTLETT et al, 2004; VERSTRAETEN et al, 2004; FERRINI-STRAMBI et al, 2003; DÉCARY et al, 2000). As hipóteses mais aceitas para explicar essa disfunção cognitiva são a fragmentação do sono e a hipóxia intermitente (YUSOP et al, 2017; GAGNON et al, 2014; MATHIEU et al, 2008; BEEBE& GOZAL, 2002; DÉCARY et al, 2000).

A fragmentação do sono é a variável, relacionada a cognição, mais estudadana apnéia do sono. Quanto mais grave for a fragmentação do sono, mais comprometidas estarão as performances nos testes de atenção e de vigilância, além de comprometimento da memória e aprendizagem (BUCKS et al, 2013; THOMAS et al, 2005; MORISSON et al, 2001; BÉDARD et al, 1991). O sono fragmentado acarreta um aumento nos níveis sistêmicos de marcadores de estresse oxidativo e inflamação, esta última levando a alterações na substância cinzenta de determinadas regiões cerebrais que contribuem para o déficit cognitivo (NAIR et al, 2011; MONTPLAISIR et al, 1992). A arquitetura do sono, e mais especificamente a porcentagem de cada estágio do sono, impacta o desempenho cognitivo diurno de todos os indivíduos, principalmente dos apneicos. Esses indivíduos apresentam frequentemente microdespertares com consequente redução no SOL e do sono REM, independentemente do tempo total de sono (TTS) (GAGNON et al, 2014; SFORZA et al, 2004; ZHANG et al, 2003). A relação entre diminuição de sono de OL e sono REM e a redução na performance de tarefas que envolvem a memória episódica em indivíduos saudáveis, já foi documentada, contribuindo para a hipótese de que a alteração da arquitetura do sono observada na SAOS possa contribuir de forma independente para o déficit cognitivo observado nessa patologia (DIEKELMANN et al, 2012). A redução do sono de OL aumenta a atividade neuronal, com consequente aumento no acúmulo de beta-amilóide (RAMOS et al, 2016; JU et al, 2014). A fragmentação do sono é ainda a responsável pela SED nesses pacientes, contribuindo ainda mais para o déficit cognitivo (QUAN et al, 2011; MAZZA et al, 2005; SFORZA et al, 2004; LEE et al, 1999).

Estudos animais e com imagens cerebrais tem demonstrado que a apneia do sono, e mais especificamente a hipóxia intermitente, causa dano neuronal em diversas regiões cerebrais (NARDONE et al, 2016; GAGNON et al, 2014; FENG et al, 2012; BEEBE & GOZAL, 2002). A hipóxia seguida de re-oxigenação resulta em alterações similares as encontradas nas injúrias isquêmicas, com a liberação de radicais livres e um processo inflamatório local, gerando um dano endotelial e a perda da integridade neuronal, especialmente no hipocampo e no córtex frontal (LAL et al, 2012; CANESSA et al, 2011; ZHU et al, 2007; ALOIA et al, 2004; GOLDBART et al, 2003). Algumas regiões cerebrais, como hipocampo, gânglios da base, cerebelo, córtex occipital e lobos frontais e pré-frontais, são mais susceptíveis a privação de oxigênio que outras (NARDONE et al, 2016; PENG et al, 2014; FENG et al, 2012). Estudos populacionais demonstram uma associação significativa entre hipóxia e alguns déficits cognitivos, incluindo déficit na atenção, diminuição na velocidade de processamento e disfunção executiva (GAGNON et al, 2014; QUAN et al, 2011; BEEBE & GOZAL, 2002; DÉCARY et al, 2000; JOKINEN et al, 1995; NAËGELÉ et al, 1995; BÉDARD et al, 1991). A relação direta entre a gravidade da hipóxia e o prejuízo na memória foi evidenciado, porém em poucos estudos (TWIGG et al, 2009; ALOIA et al, 2004; FINDLEY et al, 1986). Modelos animais demonstram que a hipóxia intermitente está associada com déficit no componente executivo da atenção e a uma vulnerabilidade a perda neuronal, particularmente no lobo frontal (GAGNON et al, 2014; MCCOY et al, 2010; GOZAL et al, 2001). Além do dano neuronal em regiões cerebrais específicas, é proposto que alterações na permeabilidade da barreira hemato-encefálica, causadas pela hipóxia, possam impactar a neuroplasticidade contribuindo para os déficits cognitivos (KERNER & ROOSE, 2016; LIM & PACK, 2014; ZLOKOVIC, 2008; SCHOCH et al, 2002).

É importante ressaltar que comorbidades associadas a SAOS, como obesidade, diabetes, hipertensão, insuficiência cardíaca e acidente vascular cerebral (AVC), têm sido identificados como fatores que contribuem de forma independente para a fragmentação do sono e para os déficits cognitivos dessa população (KRYSTA et al, 2017; LAGROTTE et al, 2016; LAL et al, 2012; PANOSSIAN & VEASEY, 2012; ALCHANATIS et al, 2008). A idade também sido associada a um pior perfil cognitivo nesses pacientes (GAGNON et al, 2014; ALCHANATIS et al, 2008; MATHIEU et al, 2008). Cosentino e colaboradores (2008) evidenciaram ainda que indivíduos apneicos portadores do alelo ApoE4 apresentam um déficit mais acentuado na memória de

trabalho do que os indivíduos que não são portadores desse mesmo alelo. No entanto, esse efeito genético na função cognitiva não foi observado em indivíduos saudáveis (NIKODEMOVA et al, 2013; COSENTINO et al, 2008).

a) Atenção

O conceito de atenção é complexo e multifacetado, sendo geralmente subdividida em atenção concentrada, dividida e alternada. A atenção concentrada refere-se à capacidade em selecionar apenas uma fonte de informação diante de vários estímulos distratores em um tempo predeterminado. A atenção alternada é a capacidade de focar ora em um estimulo ora em outro, por um determinado período de tempo. Já a atenção dividida é a capacidade de focar em dois estímulos simultaneamente, permitindo a execução de múltiplas tarefas (LEZAK, 2004). Vários estudos e metanálises têm demonstrado que pacientes apneicos- apresentam déficits nos 3 componentes da atenção (BUCKS et al, 2013; MAZZA et al, 2005; ALOIA et al, 2004; BEEBE & GOZAL, 2002). Estudos sugerem que esse déficit atencional possa influenciar outros aspectos da cognição, levando a uma provável piora nas funções executivas e na memória episódica (MATHIEU et al, 2008; MAZZA et al, 2005; VERSTRAETEN & CLUYDTS, 2004; VERSTRAETEN et al, 2004; O'DONNELL, 2002). Alguns autores reavaliaram a atenção após o tratamento com pressão positiva continua em vias aéreas (CPAP), considerado padrão-ouro para as apneias moderadas e severas, e concluíram que não houve melhora na atenção concentrada e na atenção dividida, o que sugere que a SAOS cause um dano permanente nas regiões cerebrais envolvidas nesta função cognitiva (LAU et al, 2010; ALOIA et al, 2004; FERRINI-STRAMBI et al, 2003). O corpo estriado é uma das regiões cerebrais envolvidas no processo da atenção, principalmente na aquisição de novas habilidadese essa estrutura subcortical é extremamente sensível a hipóxia noturna (MATHIEU et al, 2008; PEIGNEUX et al, 2000; MALLARD et al, 1995).

b) Funções Executivas

É um conceito complexo que engloba várias capacidades cognitivas que incluem: Controle inibitório, memória de trabalho, planejamento, flexibilidade cognitiva, tomada de decisões, fluência, criatividade e categorização (ALVAREZ & EMORY, 2006; GAGNON et al, 2004). Olaithe e Bucks (2013) realizaram uma metanálise onde foi observado um declínio nas funções executivas de pacientes com SAOS, para todos os domínios avaliados. Nas tarefas que avaliam controle inibitório, que é a capacidade de interromper uma resposta automática a um determinado

estímulo, os pacientes apneicos apresentaram maior número de erros ou um aumento no tempo de reação quando comparados com pacientes saudáveis (NAËGELÉ et al, 1995). A flexibilidade cognitiva é a capacidade de mudar de uma estratégia cognitiva ou comportamental para outra. Em vários estudos os pacientes com apnéia do sono demonstram uma redução nessa capacidade (REDLINE et al, 1997; NAËGELÉ et al, 1995; BÉDARD et al, 1991). Já a memória de trabalho se refere ao componente das funções executivas responsável por reter, manipular e evocar informações, as quais serão disponibilizadas para outros processos cognitivos.

Segundo o modelo proposto por Baddley e Hitch (1974) as funções executivas englobam uma circuitaria executiva central que trabalha em conjunto com subsistemas, a alça fonológica e a alça visuo-espacial (GAGNON et al, 2014; MIYAKE & SHAH, 1999). Estudos usando o teste de dígitos demonstraram que esta função se encontra comprometida na SAOS e ainda Saunamãki e Jehkonen (2007) concluíram que a memória de trabalho é a função executiva mais comprometida nesses pacientes, independentemente da natureza da informação (SAUNAMÃKI & JEHKONEN, 2007; DÉCARY et al, 2000; REDLINE et al, 1997; NAËGELÉ et al, 1995). A resolução de problemas envolve a avaliação e posterior seleção na sequência de ações para atingir um objetivo, e também se encontra prejudicada na apneia do sono (GAGNON et al, 2014; LEZAK et al, 2004). Outras funções executivas como velocidade de processamento, fluência e categorização também são comprometidas nos pacientes apneicos, independente da capacidade linguística (FERRINI-STRAMBI et al, 2003; NAËGELÉ et al, 1995; BÉDARD et al, 1991). A despeito do tratamento com CPAP, a função executiva desses pacientes não retorna ao normal, sugerindo novamente que haja um dano cerebral permanente (DÉCARY et al, 2000; VALENCIA-FLORES et al, 1996; BÉDARD et al, 1993).

Estudos utilizando ressonância nuclear magnética (RNM) associada a morfometria por voxel em pacientes com apnéia do sono, observaram uma redução na densidade da substância cinzenta nas seguintes regiões cerebrais: lobos parietal, frontal e temporal, hipocampo, amigdala, cingulado anterior, núcleo caudado e cerebelo (KERNER & ROOSE, 2016; NARDONE et al, 2016; FERRINI-STRAMBI et al, 2013; YAOUHI et al, 2009; MORRELL et al, 2003). Posteriormente, essa redução na densidade da substância cinzenta no hipocampo, núcleo caudado e córtex frontal foi associado a alterações na memória episódica, atenção e funções executivas (KERNER & ROOSE, 2016; CANESSA et al, 2011; TORELLI et al, 2011; GALE &

HOPKINS, 2004). Mais recentemente, estudos utilizando tensor de difusão evidenciaram alterações na substância branca de diversas regiões, como medula, cerebelo, lobo frontal, temporal e occipital, ínsula, sistema límbico, corpo caloso e coroa radiada, podendo estarem relacionada a déficits cognitivos específicos e também a alterações no humor (KERNER & ROOSE, 2016; CASTRONOVO et al, 2014; KUMAR et al, 2012; MACEY et al, 2008; ZIMMERMANN & ALOIA, 2006; BEEBE & GOZAL, 2002). Imagens funcionais, como tomografia por emissão de pósitrons (PET), cintilografia de perfusão cerebral (SPECT) e RNM com espectroscopia, na SAOS demonstram hipoperfusão e/ou hipometabolismo no córtex pré-frontal, junção temporo-parietal, pré-cuneo, cúneo, giro cingulado e hipocampo (FERRINI-STRAMBI et al, 2013; THOMAS et al, 2005). Barllett e colaboradores (2004) utilizaram a RNM com espectroscopia em indivíduos com SAOS e compararam com controles saudáveis, observando uma redução nos níveis de creatina hipocampal associado a uma queda na performance na avaliação cognitiva. A creatina exerce um papel na homeostase cerebral, tendo, portanto, propriedades neuroprotetoras e potencializando as habilidades cognitivas (BARLLETT et al, 2004; RAE et al, 2003; WYSS & KADDURAH-DAOUK, 2000). A SAOS, portanto, não pode ser vista como uma desordem especifica do lobo frontal e temporal, uma vez que o déficit neuronal envolve várias regiões corticais e subcorticais (MATHIEU et al, 2008; AYALON et al, 2006; MACEY et al, 2002).

1.4 SONOLÊNCIA EXCESSIVA DIURNA E DEPRESSÃO

A Hipersonolência, amplamente definida como sonolência excessiva diurna (SED), é a incapacidade de ficar acordado e alerta nos maiores episódios de vigília durante o dia, com o sono ocorrendo de forma involuntária ou em horários inapropriados quase diariamente por pelo menos 3 meses (ICSD-3, 2014). Apresenta um papel significativo na patogênese, avaliação e tratamento dos transtornos de humor (PLANTE, 2017; PLANTE et al, 2017; REYNOLDS, 2011). A relação bidirecional entre depressão e insônia já é bem conhecida (KRYSTAL, 2012); por outro lado, poucas pesquisas são realizadas com o objetivo de estudar a relação entre a sonolência excessiva diurna e a depressão, embora a presença da sonolência esteja relacionada a maior resistência medicamentosa, recorrência, maior gravidade nos sintomas depressivos, risco aumentado de suicídio e incapacidade funcional (HAYLEY et al, 2013; FITZGERALD et al, 2011; KAPLAN et al, 2011; KAPLAN &

HARVEY, 2009; GOLDSTEIN et al, 2008; ZIMMERMANN et al, 2005). Estudos mais recentes demonstram uma relação longitudinal bidirecional entre sonolência diurna e depressão e a principal limitação da maioria desses estudos é avaliar longitudinalmente essa relação, uma vez que a sonolência é um sintoma que pode flutuar ao longo do curso da doença (LAGROTTE et al, 2016; FERNANDEZ-MENDOZA et al, 2015; THEORELL-HAGLÖW et al, 2015; JAUSSENT et al, 2011; CHELLAPPA & ARAUJO, 2006; SILBER, 2001; HUBLIN et al, 1996). Bixler et al (2005) conduziram um estudo onde foram avaliados 16.500 indivíduos nos EUA e encontraram queixa de SED em 8,7% deles. Além disso a relação entre SED e depressão foi mais intensa (OR=3,12) do que a relação entre SED e obesidade e distúrbios respiratórios do sono (LAGROTTE et al, 2016; HAYLEY et al, 2013; CHELLAPPA et al, 2009; BIXLER et al, 2005). O sistema serotoninérgico tem um importante papel na regulação do sono e sua ação no córtex pré-frontal tem relação com os transtornos de humor. Essa interrelação atua como mais um fator de vulnerabilidade ao desenvolvimento da depressão. LaGrotte e colaboradores (2016) demonstraram que a SED é um forte preditor de depressão, dado já relatado por autores prévios (LAGROTTE et al, 2016; TSUNO et al, 2007; BIXLER et al, 2005; QUAN et al, 2005; BRESLAU et al, 1997). A hipótese mais aceita para explicar essa relação associa a genética com os sistemas monoaminergicos e circadianos, relacionados as respostas estressoras ao despertar e a subsequente hiperatividade do eixo HHA, ou alternativamente, mediado pelo aumento na ativação dos mecanismos do sono REM (DAUVILLIERS et al, 2013; MONTELEONE & MAJ, 2008). Outro mecanismo fisiopatológicobastante estudado é a associação da SED com um processo inflamatório crônico, leve, sugerindo que a sonolência associada ou não a SAOS, possa ser um sinal precoce de inflamação levando a depressão (LAGROTTE et al, 2016; PANOSSIAN & VEASEY, 2012; MILLER et al, 2009; VGONTZAS et al, 2008; VGONTZAS et al, 1997). O sistema hipocretinérgico, que tem como principal função o controle da vigília, também apresenta relação direta com vias relacionadas ao sistema de recompensa e o humor (MONTEIRO et al, 2017). As hipocretinas, também conhecidas como orexinas, são neuropeptídios produzidos no hipotálamo lateral que levam a promoção da vigília. Existem dois receptores, receptor de orexina-1(OXR1) e receptor de orexina-2 (OXR2), que possuem afinidades diferentes para hipocretina 1 e hipocretina 2. O OXR2 se liga as duas formas com a mesma afinidade, enquanto o OXR1 tem maior afinidade pela hipocretina 1 (BOSS & ROCH, 2015;

ARENDT et al, 2014). Estudos recentes sugerem que enquanto o OXR2 está envolvido, principalmente, na regulação da vigília, o OXR1 estaria envolvido na regulação do humor, do sistema de recompensa e nas funções autonômicas (MONTEIRO et al, 2017; SCOTT et al, 2011; SAKURAI, 2007). Estudos recentes demonstram que a exposição ao estresse pode levar a um aumento nos níveis de hipocretinas 1 no hipotálamo e um aumento na expressão do OXR1 no córtex frontal, levando a uma diminuição na disponibilidade sináptica da hipocretina 1 (disfunção hipocretinérgica). Essa redução na disponibilidade sináptica da hipocretina 1 estaria então relacionada ao surgimento de sintomas depressivos e de SED (MONTEIRO et al, 2017; PICH & MELOTTO, 2014).

A SED associada aos distúrbios de humor pode ser apresentada pelo paciente como queixas subjetivas de fadiga, cochilos não-reparadores, aumento do tempo total de sono e apatia, precisando ser avaliada de forma mais objetiva. O teste das latências múltiplas do sono (TLMS) é considerado o teste padrão-ouro na avaliação da SED (LITTNER et al, 2005), no entanto não há nenhuma evidência objetiva que os pacientes com de transtornos do humor tenham uma latência média anormal nesse teste (PLANTE, 2017; DAUVILLIERS et al, 2013; ARAND et al, 2005). A sonolência nos transtornos psiquiátricos é caracterizada por latências do sono geralmente dentro do padrão da normalidade, em contraste com as sonolências secundarias a doenças do sistema nervoso central ou primárias do sono, porém com queixas subjetivas de sonolência altamente frequentes (PAUDEL et al, 2013; MAGLIONE et al, 2012; CHELLAPPA et al, 2009; FAVA, 2004; YOUNG, 2004). Na prática clínica é utilizada a escala de sonolência de Epworth (ESE), a escala mais adequada para avaliação da sonolência, uma vez que inclui situações ativas e passivas. O indivíduo é instruído a quantificar de 1 a 3 a chance de cochilar em oito circunstâncias diferentes. Um somatório acima de 10 é interpretado como patológico (JOHNS, 1991). As outras duas escalas existentes, escala de sonolência de Stanford e escala de sonolência de Karolinska, são menos utilizadas uma vez que avaliam a presença de sonolência no momento da avaliação (AKERSTEDT & GILBERG, 1990; HODDES et al, 1973).

1.5 SONOLÊNCIA EXCESSIVA DIURNA E DÉFICITS COGNITIVOS

Adequada quantidade de horas de sono e uma boa qualidade do mesmo são essenciais na manutenção da atenção e da performance cognitiva em vigília (YUN et al, 2015). Assim como a insônia, a SED é um fator de risco independente para o

declínio cognitivo, principalmente no idoso (MÜLLER et al, 2017; WALLER et al, 2016; JAUSSENT et al, 2011; RAFFAITIN et al, 2011), estando associada a diminuição na capacidade de se manter alerta, déficit de memória e diminuição da atenção, independente da faixa etária (OKAMURA et al, 2016; RAMOS et al, 2016; KILLGORE et al, 2015; HERSHNER & CHERVIN, 2014; WARD et al, 2013; JAUSSENT et al, 2012; FAUBEL et al, 2009; DÉCARY et al, 2000). Adultos jovens apresentam mais prejuízo cognitivo com a privação de sono do que os idosos, embora estes também apresentem uma piora nas tarefas relacionadas à memória (WARD et al, 2013; DUFFY et al, 2009; DURMER & DINGES, 2005; BLAGROVE et al, 1995).

Yun e colaboradores (2015) avaliaram a atenção concentrada em indivíduos com queixa de sonolência excessiva diurna, através de um protocolo utilizando o teste de vigilância psicomotora (PVT). O PVT é um teste simples, realizado com um dispositivo portátil, no qual são verificadas as respostas a estímulos apresentados de forma randomizada. Eles observaram que a sonolência está relacionada a lentidão psicomotora e diminuição na capacidade de manter a atenção (YUN et al, 2015). No estudo realizado por Jaussent e colaboradores (2012) a SED foi significativamente associada a um aumento de 30% no risco de declínio cognitivo global avaliado pelo mini exame do estado mental (MINI-MENTAL), independente das características sociodemográficas, comportamentais e clínicas, das medicações hipnóticas prescritas e também do genótipo APOE (JAUSSENT et al, 2012).

A presença de SED em pacientes idosos com alguma evidência de declínio cognitivo poderia ser um sintoma precoce de lesões em áreas cerebrais responsáveis pelo controle do ciclo circadiano. Ela pode ainda fazer parte da síndrome adinâmica observada em estágios iniciais da demência (JAUSSENT et al, 2012). Uma vez que a sonolência diurna é ainda considerada um fator de risco para eventos cardiovasculares fatais e não-fatais, assim como para demência vascular, podemos sugerir que os eventos vasculares possam explicar a relação entre SED e déficit cognitivo, pelo menos no idoso (BLACHIER et al, 2012; JAUSSENT et al, 2012; ELWOOD et al, 2011; EMPANA et al, 2009).

1.6 NEUROANATOMIA E NEUROTRASMISSÃO DA DEPRESSÃO E DA COGNIÇÃO

Os sistemas serotoninérgico, noradrenérgicos, dopaminérgico, glutamatérgico e colinérgico apresentam evidências relevantes tanto na fisiopatologia dos transtornos

de humor como nas funções cognitivas. O sistema colinérgico é responsável por mediar múltiplos processos cognitivos, incluindo memória e atenção (GRAEF et al, 2010; BARTUS et al, 1982). Em roedores e primatas não-humanos, lesões no núcleo basal de Meynert, rico em projeções colinérgicas, resulta em déficits nas tarefas que avaliam aprendizado e memória (NARDONE et al, 2016; MURRAY & FIBIGER, 1985). Estudos farmacológicos em humanos indicam que tanto os receptores muscarínicos quanto os nicotínicos apresentam um papel na decodificação de novas memórias (NARDONE et al, 2016; HASSELMO, 2006). O processo atencional também é mediado pelo sistema colinérgico que facilita o processamento da informação (NARDONE et al, 2016; FUREY et al, 2008).

Evidências sugerem o envolvimento do sistema serotoninérgico nos transtornos de humor e na função cognitiva. Quando é realizado o teste de supressão aguda de triptofano (aminoácido precursor da serotonina) em parentes de primeiro grau de pacientes bipolares são observados sintomas depressivos, impulsividade e piora do desempenho em testes cognitivos (SOBCZAK et al, 2002; QUINTIN et al, 2001). Esses achados sugerem que esse sistema possa modular tanto o humor quanto a cognição (OGREN et al, 2008; TENG et al, 2008).

A disfunção do sistema noradrenérgicos está relacionado a sintomas depressivos, como anedonia, anergia e perda de libido, e ainda a sintomas cognitivos, uma vez que este sistema é responsável pela manutenção do estado de ativação dos sistemas relacionados aos circuitos da memória, atenção e concentração (TENG et al, 2008; BERRIDGE & WATERHOUSE, 2003).

Com relação ao sistema dopaminérgico, duas vias estão relacionadas ao humor e a cognição: o sistema mesolímbico, localizado no tegmento ventral cerebral e com conexões para a maior parte do sistema límbico (núcleo accumbens, amígdala, hipocampo), responsável pela regulação de expressões emocionais, aprendizado e reforço positivo; e a via mesocortical, localizada no tegmento ventral mesocortical, com conexões para regiões corticais órbito-frontais e pré-frontais, que auxilia na regulação da motivação, concentração e iniciação de tarefas cognitivas executivas complexas (TENG et al, 2008; SEAMANS &YANG, 2004).

2 JUSTIFICATIVA

Vários estudos têm sido realizados com o objetivo de investigar a relação entre SAOS e depressão, porém essa relação ainda é pouco compreendida. Estas duas patologias apresentam sintomas em comum, como fadiga, sonolência, apatia, déficit cognitivo, entre outros. Sabe-se que o déficit cognitivo é um dos sintomas depressivos que mais contribui para um pior prognóstico com menor aderência ao tratamento medicamentoso e maior risco de suicídio (MARTINEZ-ARAN et al, 2009; WESTHEIDE et al, 2008). Partindo-se das recentes evidencias cientificas que correlacionam bidirecionalmente os transtornos do sono, do humor e déficit cognitivo, esta dissertação justifica-se pela necessidade de melhor compreensão sobre como se dá a relação entre depressão, apneia e funções cognitivas, assim como os mecanismos neurobiológicos provenientes dessa relação.

3 OBJETIVOS

O objetivo deste estudo é investigar se o alto risco de apnéia do sono em pacientes com depressão influencia a gravidade dos sintomas, a queixa de sonolência diurna e as funções cognitiva relacionadas a atenção, memória de trabalho e velocidade de processamento.

4 HIPÓTESES

A hipótese do presente estudo é que o grupo de pacientes com alto risco de SAOS tenha maior gravidade nos sintomas de depressão, maior nível de sonolência diurna e menores níveis cognitivos.

5 ESTUDOS REALIZADOS NA DISSERTAÇÃO

O primeiro artigo teve como objetivo avaliar se o alto risco de SAOS em pacientes com depressão influencia na gravidade dos sintomas, na queixa de sonolência diurna e nas funções cognitivas, mais especificamente a atenção, memória de trabalho e velocidade de processamento. O estudo abordou 16 pacientes com depressão, sintomáticos, em tratamento com antidepressivo (sendo 04 pacientes em uso de inibidor de recaptação de serotonina e noradrenalina, e os outros 12 em uso de inibidor de recaptação de serotonina), e avaliou a probabilidade de SAOS. Os pacientes foram divididos em 2 grupos, baixa e alta probabilidade de apneia, com posterior avaliação dos sintomas depressivos, da sonolência e das funções cognitivas supracitadas.

O segundo artigo realizado foi uma revisão sobre a relação da hipocretina com a ansiedade, o estresse, e a depressão. A hipocretina é um neuropeptídeo hipotalâmico que atua na regulação de diversas funções fisiológicas, sendo o controle da vigília o mais importante deles. O sistema hipocretinérgico tem relação direta com vias relacionadas ao humor e sistema de recompensa, além da interação com a circuitaria do estresse. Foram discutidas as expressões dos receptores de hipoccretina, as regiões anatômicas envolvidas nessa expressão e a regulação do humor por este neuropeptídeo.

ARTIGO 1

Does obstructive sleep apnea syndrome affects daytime sleepiness and cognitive processing in patients with depression?

Does obstructive sleep apnea syndrome affects daytime sleepiness and cognitive processing in patients with depression?

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Abstract

Objectives: Patients with depression has 20% of chance of sleep disturbance, especially obstructive sleep apnea, and this can lead to a worse cognitive function in this patients. The objective of this study was to investigate if the presence of obstructive sleep apnea affects daytime sleepiness and cognitive processing in patients with depression.

Methods: Were evaluated 16 individuals (3M and 13F) with depression, using the Epworth Sleepiness Scale, Berlin Questionnaire Sleep Apnea and neuropsychological tests for attention, verbal fluency, working memory and speed processing.

Results: Subjects in higher risk of obstructive sleep apnea showed higher leves of depression severity, higher sleepiness and poor cognitive performance.

Conclusions: This study demonstrated that subjects with depression in higher risk of obstructive sleep apnea will have more daytime sleepiness and poor cognitive performance, and these symptoms can negatively influence the course of depression.

Keywords

Depression, obstructive sleep apnea, excessive daytime sleepiness, cognitive deficit

Introduction

Depression is among the most common psychiatric disorder and its lifetime prevalence is approximately 17% [1]. It has been considered a leading cause of disability worldwide, with low working capacity, social adjustment and significant impairment [1; 2]. Some of the cognitive difficulties are impairments in memory, attention, cognitive flexibility anddecision-making. These symptoms commonly persist after diseaseremission, increasing the risk of recurrence [3]. In addition, around 20% of patients in remission report impairments in concentration and decision-making [4]. There are several questions about the expression of cognitive impairment in depressive patients, as duration of symptoms, their implications and the role of antidepressants [2]. It is well known that serotonin is implicated in the regulation of cognitive flexibility, impulsivity and attention, and that some cytokines and neuromodulators also play a role in cognition [2; 5]. However, the nature of the deficits in executive functions associated with depression remains unclear [6]. Therefore, these symptoms should be accompained during the course of the disease.

Some studies have demonstrated a relationship between sleep disorders and cognitive function [7]. Physiological and behavioral studies have shown that, in the general population, there is a relationship between sleep and hippocampal function, i.e., memory consolidation [7]. One of the daytime symptoms of sleep disorders, like obstructive sleep apnea syndrome (OSAS), is the hypersomnolence; broadly define as excessive daytime sleepiness (EDS). The EDS is a tendency to fall asleep despite volitional attempts to remain alertand commonly also occurs in psychiatricdisorders, mainly depression, although this relationship is not well estabilished [8; 9*;* 10]. Excessive daytime sleepiness has been found in 7-8% of patients with depression and it is known that is associated with treatment resistance, increased risk of suicide, functional impairment and symptomatic relapse [11; 12]. Some reports demonstrated a bidirectional and longitudinal relationship between depression and EDS [8*;* 12; 13; 14]. EDS slows responses and increases errors in attention tasks [15]. In a population-based study of 1026 older adults, EDS was a risk factor for reduced attention and memory [16]. Several studies suggested a strong association between greater level of depressive symptoms and subjective EDS [10; 17; 18; 19] and some of them have shown that extremely low or high sleep durations were associated with poor cognitive performance and represent a risk for depressive disorders [9; 10; 20]. Insomnia and EDS seem to be independent risk factors of depression and cognitive decline in elderly individuals; they are associated with lower alertness, attentional deficits and memory impairment not only in the elderly [11]. Sleep disorders can result in wake state instability and a decreased ability to sustain one's attention and an increased duration of lapses [7].

Obstructive sleep apnea syndrome (OSAS) is a common disease, affecting about 2-4% of the adult population, which is characterizedby frequent breathing cessation and/or reduction of airflow due to partial or complete upper airway obstructions that occur during sleep and are usually associated witha reduction in blood oxygen saturation [21*;* 22]. The pathophysiology of OSAS is complex and the exact mechanism that causes cognitive dysfunction is still unclear.Recent data has identified attention, episodic memory, working memory and executive function as the most affected cognitive domais in OSAS [21*;* 23]. Several studies have investigated the association of OSAS and depression; however, the relationship is still poorly understood [24]. Knecht et al. conducted a study where they avaluated 42 patients with heart failure without OSAS and 138 patients with heart failure and OSAS, this last group performed worse on tasks related to global cognitive function and attention as compared to the other group [25].

The objective of this study was to assess if sleep disorders in depressive patients could be associated with impairments in attention, working memoryand speed processing. The specific aims of this study are: (1) to investigate if obstructive sleep apnea syndrome affects symptoms of depression, sleepiness and cognitive functions. More specifically, we will examine the effects of high and low risk for apnea on symptoms of depression, sleepiness and, attention, working memory, and speed processing.

Methods

Sample

Sample was composed of 16 individuals (3M and 13F). Senior researchers evaluated them, using the follow diagnostic and neuropsychological instruments: Mini International Neuropsychiatric Interview (MINI), the Beck Depression Inventory (BDI-II), Epworth Sleepiness scale (ESS), Berlin Questionnaire Sleep Apnea (BQSA), Working Memory Index (WMI), Speed Processing Index (SPI) and Psychological Battery for Attention (PBA). Inclusion criteria are aged between 18 and 59 years, diagnosis of depression according to the DSM-5 criteria, completed high schoolas minimum level of education and being in use of antidepressant. The exclusion criteria are being on more than one antidepressant, using psychostimulants such as methylphenidate or lisdexamphetamine, pregnant or breastfeeding women, severe psychiatric disorders such as psychotic signs and symptoms, obsessive-compulsive disorder, hypomanic/manic episodes, severe personality disorder, neurological disorders, mental retardation, epilepsy, alcohol abuse and other drugs.

Experimental Procedures

All the patients were submitted to the psychological and neuropsychological tests in a single moment. All assessments were conducted at the Laboratory of Panic and Respiration and took around 2 hours.

Instruments

For clinical assessment, were used ESS and BQSA, and for psychological and neuropsychological assessment, the instruments used were BDI-II, WMI, SPI and PBA.

To verify the possibility of OSAS it was used the BQSA. This questionnaire is composed of 10 itens, organized in three categories reffering to snore and apneas (5 itens), excessive daytime sleepiness (4 itens) and hypertension/obesity (1 item). The determination in high or low risk of OSAS (i.e., HOSAS and LOSAS) is based on the answers of each category.

To evaluatedepression symptoms participants filled BDI-II, a scale extensively used worldwide, that is validation for Brazilian population showed temporal stability and was internally consistent and valid for predicting the presence of depressive symptoms. It was considered able to participate the study those individuals who presented a score ≥14. BDI II is a self-rating instrument with 21 questions that assesses different groups of symptoms by asking the patient to respond each question weighting it in a scale from zero to three, basing his answer in the symptom severity. The total score is the sum of all the 21 questions, and the subject is classified as minimal depression (0-13), mild depression (14-19), moderate depression (20-28)and severe depression (29-63).

ESS was used to assess the excessive daytime sleepiness, measuring the general level of daytime sleepiness or sleep propensity in adults. It is a brief self-administered questionnaire that asks the subject to rate on a scale of 0-3 the chances that, over "recent times", he would have dozed in eight specific situations that are commonly met in daily life (0 = would never doze; 3 = high chance of dozing). ESS socre is the sum of eight itens scores and can range fron 0 to 24. A score ≥10 is considered positive for excessive daytime sleepiness [26].

With respect to the neuropsychological measures, were used the WMI, SPI, and PBA.WMI corresponds to assessment of the functions: Arithmetic, Digit Span and Letter-Number Sequencing. The Arithmetic subscale contains 20 questions about arithmetic problems, that the examiner has to solve mentally in a determined period. The Digit Span subscale contains 7 items in the direct order and 7 in indirect order that have to be exactly repeated. The Letter-Number Sequencing subscale is a series of numbers and letters presented in oral form that has to be repeated putting first the numbers in ascending order and after the letters in alphabetic order [27].

For attention evaluation, was used the BPA, which is a Brazilian battery for evaluation of the attentional function, divided in 3 categories: alternating, divided and sustained attention. To evaluate the sustained attention

(SA) is use an instrument that contains 400 stimulus, distributed in 20 lines with 20 stimulus in each. Each odd line has 7 target stimulus and 13 distractors, while each pair line has 5 target stimulus and 15 distractors. On top of the evaluation sheet, it has one model that the evaluated person has to point out. The test has 2 minutes of duration and the measure correspond to the sum of the target stimulus pointed out less the mistakes and omissions committed. In concern to divided attention (DA) the instrument that were used contains 400 stimulus, distributed in 20 lines with 20 stimulus in each. Each line has 6 target stimulus and 14 distractors. On top of the evaluation sheet, it has three models that the evaluated person has to point out. The test has 4 minutes of duration and once again, the measure correspond to the sum of the target stimulus pointed out less the mistakes and omissions committed. The alternating attention (AA) instrument has the same 400 stimulus, distributed in 20 lines with 20 stimulus in each. Each odd line has 5 target stimulus and 15 distractors, while each pair line has 7 target stimulus and 13 distractors. In this test, each line has its own model that the evaluated person has to point out. The test has 2 minutes and 30 seconds of duration and like the others the measure correspond to the sum of the target stimulus pointed out less the mistakes and omissions committed[28].

SPI is related to attention, memory and concentration to immediately process the visual information and will evaluate the resistance to distraction. It was used code and symbol search to evaluate SPI. In the code search test there is a series of numbers, each one associated with a symbol; using a key, the subject needs to write the symbol associated with the number. The subtest symbol search is composed of a series of couple symbol groups, each one consisting of a model group and a search group, and the subject needs to indicate if the model symbol it is on the search group or not [29].

Statistical Analysis

A homoscedasticity and normality analysis of the data were performed by the Levene and Shapiro-Wilk tests, respectively. It was used a t-test for independent samples to compare their and verify differences between groups. In both analyzes the level of significance was adjusted at $p < 0.05$.

Results

Table 1 presents the characterization of our sample. Patients were divided into the groups according to their classification in OSAS, i.e., HOSAS (n=8) or LOSAS(n=8).

Table 1. Sample charactherization

Features	HOSAS		LOSAS	
	M±SD	%	M±SD	%
Age (years)	35.62±10.33	-	33.12±9.11	-
Education (years)	69.58±13.98	-	71±12.25	-
Gender	-	7F (87.5)/1M (12.5)	-	7F (87.5)/1M (12.5)

HOSAS patients showed higher levels of depression severity in BDI-II compared to LOSAS (37.5±9.2 vs 21.8±4.9; t= 4,206; p= 0,001; table 1), as well as higher sleepiness compared to LOSAS (12.2±2.8 vs 8.3±3.8; t= 2.283; p= 0.03; table 2).

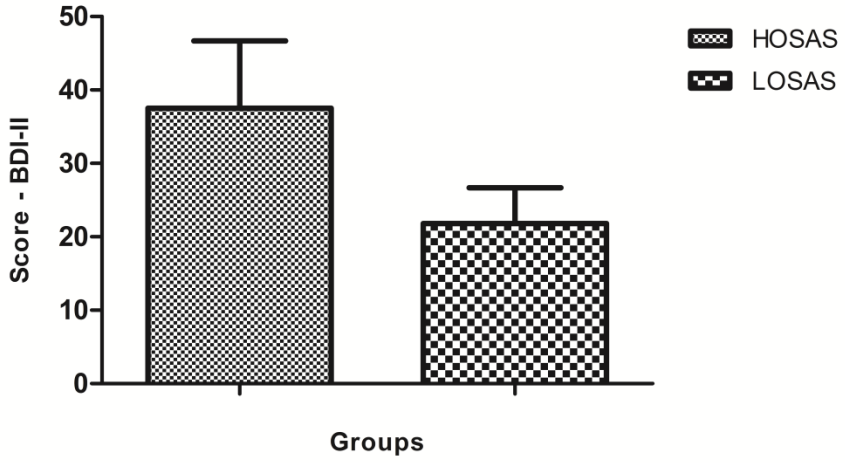

Figure 1. Scores of BDI-II for HOSAS and LOSAS groups.

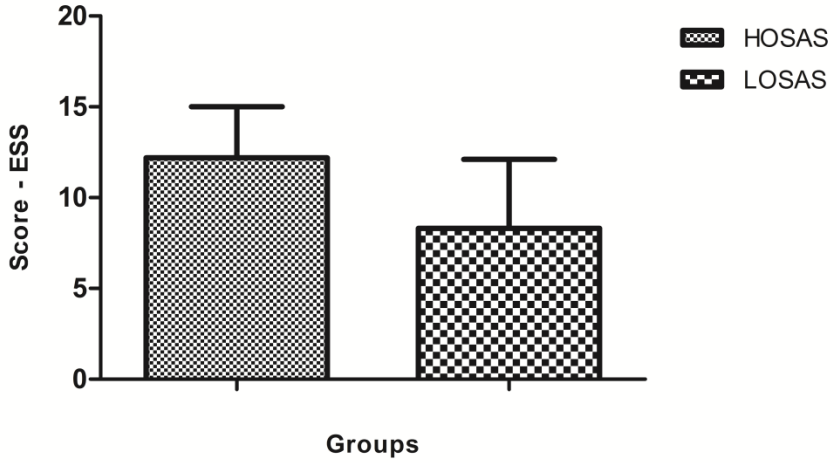

Figure 2. Scores of ESS for HOSAS and LOSAS groups

When compared WMI between the HOSAS and LOSAS groups, HOSAS showed lower levels (88.2±10.0) compared to LOSAS (101.2±6.0; t= -3,18; p= 0,007; table 3).

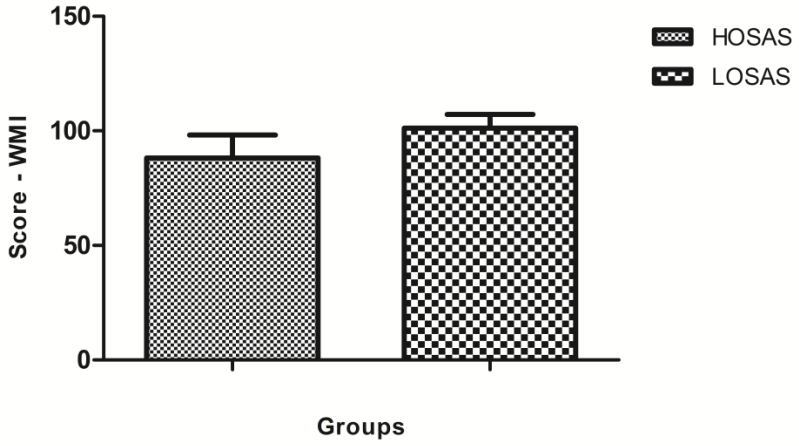

Figure 3. Scores of WMI for HOSAS and LOSAS groups.

With regard to SPI, HOSAS showed lower levels (110.0±8.0) compared to LOSAS (120.0±5.8; t= -2.853;p= 0.013; table 4).

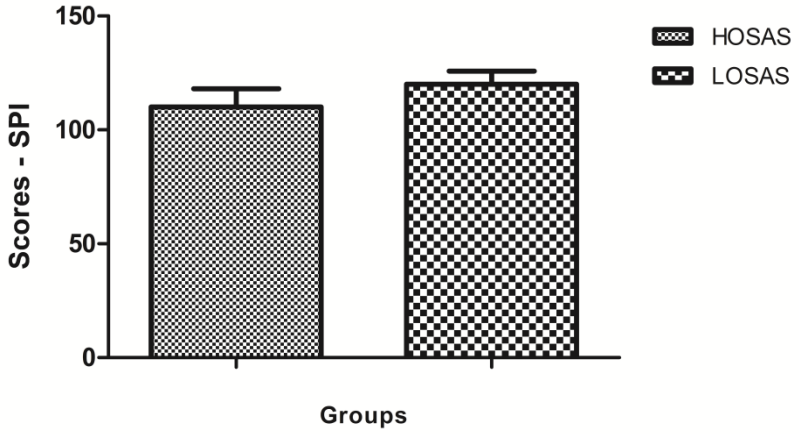

Figure 4. Scores of SPI for HOSAS and LOSAS groups.

With regard to DA, HOSAS showed lower levels (80.8±25.5) compared to LOSAS (103.2±6.9; t= -2.337; p= 0.035; table 5A). When compared SA between the HOSAS and LOSAS groups, HOSAS showed lower levels (69.87±18.65) compared to LOSAS (92.87±14.04; t= -3,292; p= 0,005; table 5B). At last, when analyzed AA between HOSAS and LOSAS groups, HOSAS showed lower levels 83.2±16.4) compared to LOSAS (100.2±15.4; t= -2131; p= 0.05; table 5C).

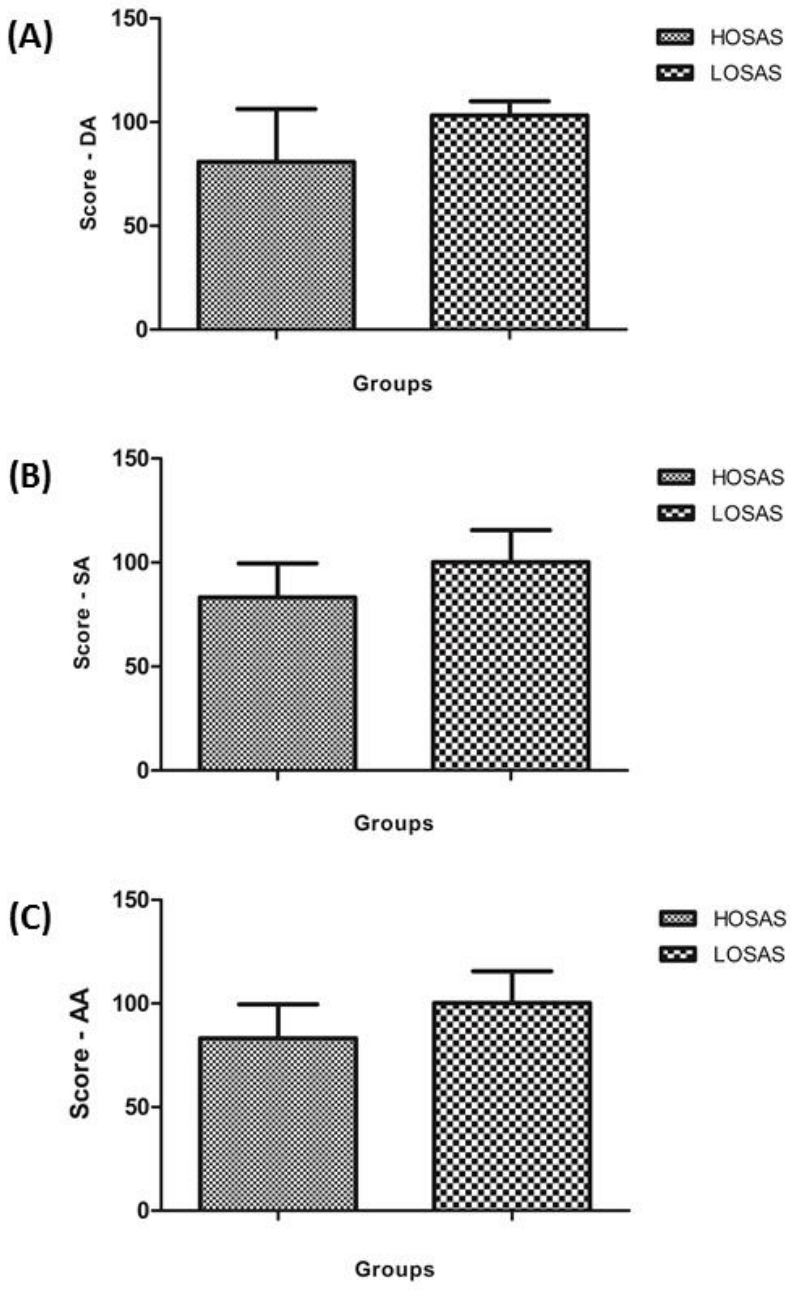

Figure 5. Scores of attention subtypes for HOSAS and LOSAS groups. A) Divided attention; B) Sustained attention and C) Alternate attention.

Discussion

This study aims to investigate if the presence of higher risk of obstructive sleep apnea syndrome could interfere on cognitive function and daytime sleepiness in depressive patients. Several studies have been made to investigate the relationship between OSAS and depression. This correlation is not well established, but it already known that prevalence of depression in patients with OSAS it`s considerable. In thisstudy,it was observed that patients with higher risk of OSAS had higher level in BDI-II. This could be explained by several mechanisms,

but sleep fragmentation and intermittent hypoxia are the most accepted ones [30]. Sleep fragmentation is the primary cause of daytime sleepiness in apneic patients leading to depressive symptoms [24; 30; 31; 32]. Daytime sleepiness is one of the most prevalent symptoms of OSAS and usually it has a direct relation with OSAS severity [21]. In this study results, this direct relation was confirmed. The patients who had higher chance of OSAS had higher sleepiness. The presence of OSAS it's associated with high levels of interleukin-16 (IL-16) and tumor necrosis factor (TNF), proinflammatories cytokines that act like mediators of daytime sleepiness and have a regulator function on mood [33; 34; 35; 36; 37]. With regard to hypoxia, some recent datas suggest that this could be associated with changes in the white matter metabolism leading to depressive symptoms [38; 39; 40].

Cognitive dysfunctions it is one of the daytime symptoms of patients with OSAS, and it is characterized by impariments of attention, episodic memory, working memory and executive functions [21]. Several studies have demonstrated that OSA subjects show impairments for all attention components (sustained, alternating and divided) and these observations were confirmed in this research [39; 41; 42; 43]. Given the severity and the extent of attentional deficits, it has been suggested that this could influence others aspects of cognitive deficits attributed to OSA, like executive functions and episodic memory [44; 45]. The executive functions allow individuals use their basic skills to perform adequately in a changing environment [46]. A recent meta-analysis reported that executive functions are impaired in OSA for all five sub-domains studied, inhibition, shifting, updating/monitoring information in working memory, generating new information and fluid reasoning and problem solving [47]. In thisstudy, were evaluated working memory and speed processing, and like previus researchs, it wasshowed that subjects in higher risk for OSA perform poorly on this two sub-domains, despite normal language skills [48; 49; 50; 51]. Saunamãki and Jehkonen also found that working memory was among the most frequently impaired components of the executive functions in this population [52].

Like depressive symptoms and severtity, several studies have aimed to understand the specific role of sleep fragmentation and intermittent hypoxemia in the aetiology of cognitive dysfunctions in OSA population [21]. According to some reviews, the more severe is sleep fragmentation, the more impaired are the performance on attention and memory [41; 53]. The sleep fragmentation changes the sleep architecture, with lower percentage of slow waves sleep and rapid eye movement (REM) sleep, what is associated with impairments in tasks involving episodic memory, even in healthy subjects. Therefore, changes in sleep architecture in OSA patients may independently contribute to their cognitive deficits [54]. The relation of daytime sleepiness, a consequence of sleep fragmentation, and cognitive dysfunction it is better understood. Evidence from narcoleptic patients indicates that cognitive performance is influenced by daytime sleepiness [55; 56]. Studies with sleep deprivation have

consistently reported that increasing daytime sleepiness lead to cognitive impairment [57; 58; 59]. Animals and brain imaging studies have found that OSA, and more specifically hypoxemia, causes neuronal damage in multiple brain regions [21; 43; 60]. This type of injury increases free radicals and inflammation, which are particularly damaging for endothelial and neuronal integrity, especially in the hippocampus and the frontal cortex [61; 62]. Large population studies have confirmed a significant association between hypoxemia and cognitive deficits, including attentional impairment, slow processing speed and executive dysfunctions [43; 50; 63]. Animal models have shown that intermittent hypoxia was associated with impairments in the execution component of attention and to a particular vulnerability to neuronal loss in the frontal lobe [62; 64].

Structural brain imaging studies using magnetic resonance imaging (MRI) combined with voxel-based morphometry in subjects with OSA, showed reduced grey matter density in distinct areas like parietal, temporal and frontal lobes, the hippocampus, the amydala, the anterior cingulate, the caudate nucleus and the cerebellum. These alterations could explain the cognitive deficits and the depressive symptoms [62; 65; 66]. More recently, diffusion tensor imaging shows abnormalities in white matter of temporal and frontal lobes, that could be associated with more specific cognitive deficits and mood disorders [67; 68].

Conclusion

Despite many challenges in studies designs, that is substancial evidence that the presence of OSA will affect the cognitive function and the daytime sleepiness of depressive patients. This study demonstrated that subjects in higher risk of OSA will have more daytime sleepiness and impairments in attention, working memory and speed processing. There was some limitations like the number of subjects evaluated, the study design (cross-sectional study) and the absence of objective sleep studies, like polysomnography (PSG) and multiple sleep latency test (MSLT), that could gave us objective measures of severity of OSA and of sleepiness.

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ARTIGO 2

Neurobiological role of hypocretin in regulation of psychiatric disorders

Neurobiological role of hypocretin in regulation of psychiatric disorders

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Abstract

Hypocretins are hypothalamics neuropeptides acting on the regulation of several physiological functions, being the control of the arousal the most important of them. The hypocretin 1 and hypocretin 2 derived from the same precursor and both bind to the orexin receptors. The hypocretinergic system has been a target of several studies that try to understand its function on the regulation of mood and behavior. The hypocretinergic system has a direct relationship with the pathways related with emotions and reward system, besides the interaction with the stress circuit. This article aims to analyze the relationship of the hypocretins with anxiety, stress and depression, through a review of the existing literature.

Keywords: Hypocretin; anxiety; depression; stress.

1. Introduction

Hypocretins, also known as orexins, are neuropeptides synthetized in the posterior lateral hypothalamus, with involvement in various physiological functions and pathological conditions [1]. The hypocretin 1 (named as orexin A) and hypocretin 2 (named as orexin B) are derived from the same precursor peptide containing 33 and 28 amino acids respectively, and which bind to the orexin receptors [2]. Orexin 2 receptors (OXR2) bind to both forms with the same affinity, whereas the orexin type 1 receptor (OXR1) displays higher affinity for hypocretin 1 [2]. Although hypocretinergic neurons are present in the posterior lateral hypothalamus, they project pathways to the central nervous system (spinal cord, brainstem, hypothalamus, thalamus, some cortical regions and limbic system) and peripheral, including vagus nerve [3]. In addition, orexin receptors have an extensive distribution suggesting a relevant role in adaptive functions and functions regulated by the limbic system (Figure 1). The distribution of these receptors is extensive and most often the subtypes overlap. However, some brain regions preferentially express a subtype, suggesting a certain degree of selectivity [3].

OXR1 expression is observed in various brain regions, including the prefrontal and infralimbic cortex, hippocampus, amygdala, dorsal striatum nucleus, paraventricular thalamic nucleus, anterior hypothalamus, dorsal raphe and locus ceruleus [4, 5]. While the OXR2 subtype is found in the amygdala, nucleus of the dorsal striatum, paraventricular thalamic nucleus, dorsal raphe and peduncle-pontine nuclei and accumbens [4, 5]. Recent studies suggest that OXR1 is involved in various functions, especially regulation of emotion, reward system and autonomic function [6] while OXR2 is mainly involved in the regulation of wakefulness [7]. This divergence in receptor functions is also observed in the regulation of mood and affect, having an important role in depression, anxiety and stress [8].

The hypocretinergic system is modulated by multiple endocrine signals and neural imputs from other areas, suggesting that this system is influenced by internal and external stimuli and is involved in several physiological functions, including the sleep-wake cycle, energetic metabolism, behavioral and neuroendocrinological responses to stress and reward system [9-11]. Diseases such as depression and anxiety, as well as conditions such as stress would affect this system, which will have the potential to modulate mood through its neuroanatomical projections and the expression of its receptors in certain brain regions [8].

Dysregulation of sleep/wake cycle predispose to metabolic and psychiatric disorders [4]. The evidences of the role of the hypocretinergic system on the modulation of several physiological functions and mental diseases emerged after the dicovery of this system, fifteen years ago, but the exact mechanism how this modulation occurs is not well known [10]. In the last decade, a significant advance was made about the complex interactions between

brain systems that control the transition of sleep and wake states [4]. Recently, a lot of research is being done with OXR1 and OXR2 antagonists promising therapeutic target and encouraging investments of the pharmaceutic industry on basics researches. The database of these pre-clinical studies are limited and the involvement of hypocretinergic system is still questionable [10]. Thus, the objective of the present study was to critically discuss the relationship between orexin and psychiatric disorders.

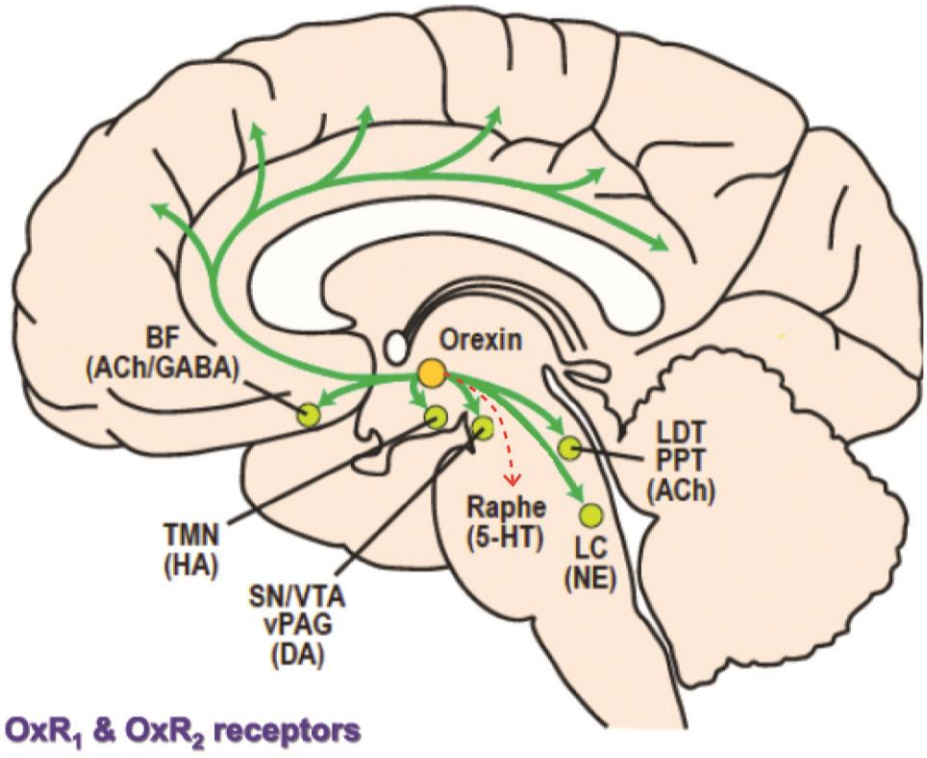

Figure 1. The distribution of the wake-modulating system in the brain. The drawing shows elements that participate in the control of waking including: Tuberommamillary nucleus (TMN; histamine [HA]), basal forebrail (BF; acetylcholine (ACh)/GABA), orexin, locus coeruleus (LC; noradrenaline [NE]), raphe nuclei (serotonin, 5-HT), sustantia nigra (SN)/ventral tegmental area (VTA) and ventral periaqueductal gray (vPGAM; dopamine, [DA]).

2. Hypocretin as regulator of waking state

The waking state is controlled by several neurobiological networks, including circadian, homeostatic influences as well as by genetic, molecular, neuroanatomical, and neurochemical elements [12-14]. For example, waking is modulated by the activity of diverse neurotransmitter systems such as noradrenaline, dopamine, serotonin, acetylcholine, histamine and hypocretin [3, 15-24] (Figure 2).A small number of hypocretinergic neurons are exclusively localized into the lateral hypothalamic area and send their projections throughout the brain as well as the spinal cord [25-27]. One might think that because of this projection pathway, the hypocretinergic system might have multiple physiological functions apart of controlling wakefulness, including motor control, drug reward, and mental health [28, 30]. In the following sections, we highlight the experimental evidence

published in the literature regarding hypocretin as mood modulator.

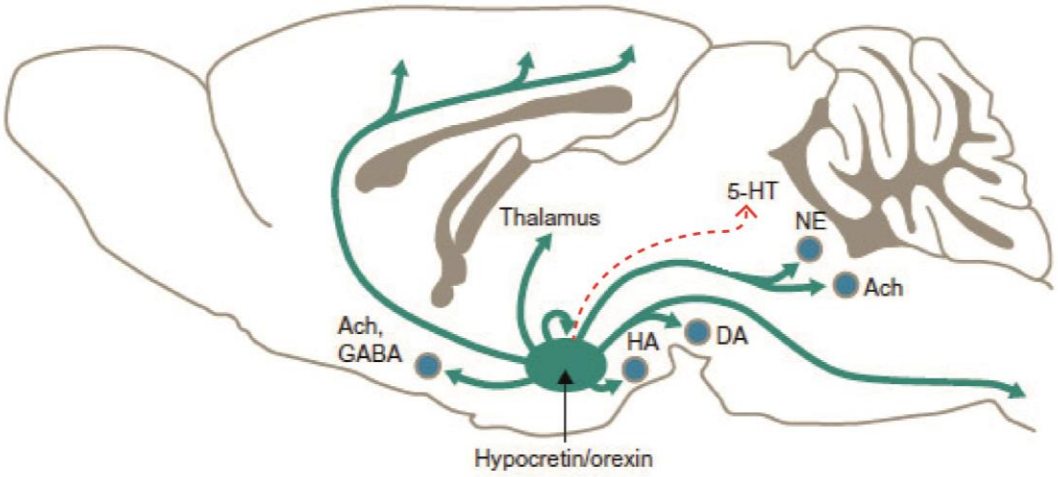

Figure 2. Schematic representation of the hypocretinergic system that modulates sleep-wake cycle. Hypocretins/orexins placed in hypothalamus send inhibitory rostral projections to thalamus and basal forebrain containing cholinergic and GABAergic neurons. Moreover, hypocretin/orexin cluster of neurons in hypothalamus sends stimulatory caudal projections to noradrenergic (NE, locus coeruleus), cholinergic (ACh, PPT/LDT), histaminergic (HA, tuberommamillary nucleus) and dopaminergic (DA) as well as serotoninergic (5-HT, raphe nuclei) nucleus.

3. Psychiatric disorders regulated by hypocretins

The hypocretinergic system has been related with narcolepsy, a disorder characterized by hypersomnolence during normal wakefulness [3, 31-35]. However, recent evidence has suggested that hypocretinergic system is linked with other health issues, such as obesity, mood, and other psychiatric disorders [28, 29, 36-39]. This system has a close relationship (functional and anatomical) with pathways that regulate the autonomic system, mood, emotions and the reward system [5].

3.1 Mood regulated by hypocretins

The relationship between hypocretin and mood disorders, specifically depression, has received special attention in recent years with divergent findings among various authors. There has been an association between OXR1 gene polymorphism and mood disorders and high hypocretin levels correlated with positive content emotions and social interaction. In addition, non-genetic factors such as chronic stress also cause hypocretin to be involved in the pathogenesis of depression [4]. The projection of hypocretinergic neurons to the hippocampus explains the involvement of this system in the learning and memory-related process of depression, known as learned helplessness [1,2,4,40].

It is possible that dysregulation of the hypothalamic-pituitary-adrenal axis (HPA), which is often

associated with major depression, is in part an inability of the paraventricular thalamic nucleus to adapt to chronic stress. More recent studies demonstrate that exposure to a stressor stimulus over a long period would lead to a downregulation of hypocretinergic activity. This early exposure to stress would increase the levels of hypocretin 1 in the hypothalamic regions and the expression of the OXR1 in the frontal cortex, thus there would be a consequent reduction in the synaptic availability of hypocretin (hypocretinergic dysfunction). In contrast, in the case of patients with depression and their reduction after treatment with anti-depressant sertraline, Salomon et al. (2003) demonstrate the opposite effect, reporting high levels of hypocretin 1 in CSF, unlike Schmidt et al. (2011) which did not show any association between depression and cerebrospinal fluid levels of hypocretin.

Two hypotheses explain these divergent findings. First, we must consider that depression is a naturally heterogenic disease, influenced by environmental, genetic and comorbid factors [4, 8]. Second, recent studies report divergent roles for hypocretin receptors, and both exert functions that counterbalanced brain regions involved in mood regulation, such as the hippocampus, frontal tegmental area and prefrontal cortex [4, 8]. In the study by Scott et al. (2011) knockout mice for OXR1 presented decrease in depressive symptoms, whereas knockout mice for OXR2 showed an increase of these symptoms.

3.2 Anxiety regulated by hypocretins

The subnuclei of the basolateral and central amygdala, the prefrontal cortex and the paraventricular thalamic nucleus are regions known to be involved in anxiety and all have hypocretinergic connections [2]. The application of hypocretin 1 or 2 in the central sub-nucleus of the amygdala, rich in hypocretinergic projections, excites the neurons of this region producing an increase in the anxious behavior [2, 11]. On the other hand, inhibition of glutamate and the action of OXR2 in the basolateral region would lead to a relief in anxiety. Studies have shown an increase in the release of hypocretin in the amygdala and in the cerebrospinal fluid of anxiety patients, suggesting a possible hyperactivity state of the hypocretinergic system in these patients [2, 11]. In these studies, the levels of hypocretin increased during wakefulness and fell during sleep, but the highest peak was during an acute emotional state, whether positive or negative.
The pre-limbic region of the prefrontal cortex would be, for anatomical and functional reasons, a potential area for the action of hypocretin in the regulation of anxiety, but no study has demonstrated this relationship. Heydendael et al. (2011) have demonstrated that the stimulation of hypocretinergic receptors in the paraventricular thalamic nucleus produces fear and anxious-like behavior and the blockade of these receptors in the same area has anxiolytic effects.

3.3 Stress regulated by hypocretins

The role of hypocretin in chronic stress occurs through the depolarization of neurons present in the paraventricular thalamic nucleus (PVN), a site rich in type 1 and 2 receptors. This nucleus plays an important role in the regulation of the neuroendocrine system and in the behavioral adaptation after a severe stressor stimulus. In chronic stress it is necessary to reduce the circadian rhythm of body temperature and the activation of the hypothalamic-pituitary-adrenal (HPA) axis, and may also be the link between circadian cycle disorders, chronic stress and depression, mainly through hypocretinergic pathways [4, 6].

Hypocretin would activate the HPA axis, including corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and corticosterone, stimulating stress behavior [9, 41]. The hypocretinergic system, in addition to receiving inputs from CRH-producing pathways, also sends projections that stimulate the brain regions responsible for the production of this hormone [10]. This evidence suggests that these two systems are involved in stress management, although acting in different brain areas. While the CRH acts on the motor cortex, the prefrontal cortex, the dorsal portions of the caudate and putamen nuclei, the cingulate and amygdala, the hypocretin will act on the nucleus accumbens, dorsal thalamus, amygdala, ventral hippocampus and frontal cortex [10]. The region that has the largest neural network of CRH stimulation to the hypocretinergic neurons is the nucleus of the dorsal striatum (BNST), belonging to the limbic system [42].

3.4 Other Psychiatric Disorders regulated by hypocretins

As regarding psychiatric disorders, schizophrenia affects approximately 1% of the world population. This disease has been managed by using pharmacological means including compounds that interact with monoaminergic transmission [43-46]. Recent data have suggested the putative role of hypocretin in modulation of schizophrenia [36]. For example, Sansa and coworkers[39] reported that patients with schizophrenia showed positive correlation with human leukocyte antigen (HLA) DQB1*06:02. Importantly, narcolepsy with cataplexy has been strongly associated with the same HLA [47].Thus, it is likely that hypocretin might be present in patients with schizophrenia. Further studies have confirmed this observation. For instance, plasma levels of hypocretin 1 in 127 patients with schizophrenia were determined. In patients, the clinical symptoms on the Positive and Negative Syndrome Scale for schizophrenia, as well as executive function by the Wisconsin Card Sorting test, were assessed. It was found that patients with schizophrenia had a significantly higher levels of hypocretin 1 compared to healthy controls [48]. These findings corroborated previous studies [49] and these results are in concordance with posterior observations [37, 50]. Beyond the neurobiological role of hypocretin on the modulation

of sleep-wake cycle, an accumulative body of evidence is suggesting the putative influence of this peptidergic system in schizophrenia. Thus, a novel and interesting approach for targeting hypocretin for the development of novel antipsychotic medications remains to be elucidated.

4. Conclusions

The hypocretin is involved in the modulation of several neurobiological systems, both central and peripheral, but the exact mechanism as this modulation occurs is not well known. New drugs involving this system are being studied. Several different chemical structures can bind to one or both hypocretin receptors. When the antagonist binds to a single receptor, it is called SORAs and dual antagonists are called DORAs. Four DORAs have undergone clinical trials: almorexant, suvorexant, filorexant and SB-649868. Only suvorexant went through phase 3 and it was filed in USA and Japan as a new treatment for insomnia in 2013 [10]. From this new development, a growing interest has been seeing toward this system and its role in modulating anxious and depressive behavior. These advances may also lead to the development of new molecules for the treatment of sleep disorders and psychiatric conditions.

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6 CONCLUSÃO

Sintomas depressivos são frequentemente relatados por pacientes com apneia do sono, e altas taxas de sintomatologia depressiva são encontradas nesses pacientes quando comparados com a população geral. Entre 15 a 56% dos pacientes apneicos são diagnosticados com depressão, contra apenas 6,6% da população geral (JACKSON et al, 2011; SCHRODER & O'HARA, 2005; KESSLER et al, 2003; REYNOLDS et al, 1989; KALES et al, 1985).A sintomatologia em comum com a depressão é um obstáculo para determinar a presença e a severidade de uma das patologias na presença da outra, tanto em pesquisas quanto clinicamente, sendo comum que a SAOS seja uma doença subdiagnosticada em pacientes depressivos.Embora alguns aspectos da relação entre sono e cognição ainda não estejam totalmente esclarecidos, as seguintes evidências já se encontram bem estabelecidas: (1) O sono REM é o período em que o material recentemente aprendido será consolidado; (2) há uma relação entre atividade colinérgica e início e frequência das fases do sono REM; (3) a consolidação da memória está relacionada à frequência de fusos no SOL. Portanto, uma patologia que cause uma alteração na arquitetura do sono, como ocorre com a SAOS, poderia levar a alterações cognitivas.

Conforme os achados no artigo 1, a presença de alto risco de apneia do sono em pacientes com depressão aumenta o grau de sonolência diurna desses pacientes, intensifica os sintomas depressivos e piorao perfil cognitivo. Os três domínios cognitivos avaliados neste artigo, memoria de trabalho, atenção e índice de velocidade de processamento, foram afetados pela alta probabilidade de SAOS. A polissonografia noturna é o exame padrão-ouro para avaliação da possibilidade de distúrbios respiratórios do sono, no entanto seu alto custo não permite seu uso de maneira ampla (BEST et al, 2013). O questionário de Berlin é uma ferramenta amplamente utilizada na avaliação clínica para a possibilidade de SAOS, com uma sensibilidade de 87% e uma especificidade de 77% (BEST et al, 2013; NETZER et al, 1999). Neste estudo, este questionário foi utilizado para acessar a probabilidade de SAOS em pacientes depressivos.

Se existe uma relação causal entre SAOS e depressão, espera-se então que os sintomas depressivos melhorem ou até mesmo desapareçam após o tratamento adequado da SAOS. A maioria dos estudos observacionais encontrou uma redução nos sintomas depressivos após o tratamento com CPAP (DIAMANTI et al, 2013; KAWAHARA et al, 2005; SCHWARTZ et al, 2005). Os poucos estudos que não

evidenciaram esta redução utilizaram apenas 2 a 4 semanas de CPAPterapia, enquanto o efeito do tratamento com antidepressivos requer tipicamente de 4 a 6 semanas ou mais para evidenciar uma resposta significativa (POVITZ et al, 2014; BARDWELL et al, 2007; HAENSEL et al, 2007; GILES et al, 2006; HENKE et al, 2001). Evidências mais recentes indicam que pacientes com SAOS que apresentam SED residual, sonolência mantida mesmo com boa aderência ao CPAP, possuem maior risco de permanência de seus sintomas depressivos (BAHAMMAM et al, 2016). Vendo esta relação de outra perspectiva, a presença de sintomas depressivos poderia impactar a aderência ao CPAP, uma vez que a depressão é associada a baixa aderência terapêutica em praticamente todas as doenças crônicas (BAHAMMAM et al, 2016; GRENARD et al, 2011; KJELSBERG et al, 2005).

No estudo 2 foi avaliada a relação da hipocretina com os transtornos psiquiátricos. A hipocretina está envolvida na regulação de diversas funções fisiológicas, sendo o controle da vigília a mais importante delas, e possui relação direta com as vias relacionadas as emoções e ao sistema de recompensa, além da interação com a circuitaria do estresse. Doenças como a depressão afetam esse sistema, que terá o potencial de modular o humor através de projeções neuroanatômicas e da expressão de seus receptores em determinadas regiões cerebrais. Recentemente, vários estudos estão sendo conduzidos com antagonistas dos receptores OXR1 e OXR2 para o tratamento de insônia e ainda para uma possível ação antidepressiva.

O mecanismo fisiopatológico envolvendo a SAOS, depressão e déficit cognitivo é complexo e pouco compreendido. A fragmentação do sono e a hipóxia intermitente, são até o momento os mecanismos mais aceitos nessa relação. A nível de neurotransmissor o sistema serotoninérgico tem um papel central subjacente como um substrato neurobiológico na regulação do humor, do ciclo sono-vigília e ainda do controle do tônus muscular das vias aéreas superiores durante o sono. O papel exato da serotonina no núcleo do hipoglosso ainda e desconhecido, lembrando que esta é uma via complexa, com múltiplos subtipos de receptores. Outros neurotransmissores como a noradrenalina e o ácido gama-aminobutírico (GABA) também estão envolvidos na regulação da vigília e do humor.

A presença de distúrbios do sono, e mais especificamente a SAOS, podem ser responsáveis pelo fracasso no tratamento medicamentoso da depressão. Dessa forma, recomenda-se que pacientes com depressão sejam triados para a possibilidade de SAOS, uma vez que a identificação desta patologia do sono e seu

tratamento adequado poderá influenciar no curso e prognóstico, não só dos sintomas depressivos, mas também do déficit cognitivo associado a depressão.

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8 APÊNDICE I – OUTRAS PRODUÇÕES RELEVANTES

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