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**ORGANIZAÇÃO DAS PROJEÇÕES DA ÁREA TEGMENTAL VENTRAL  
PARA O COMPLEXO VTA-SUBSTÂNCIA NEGRA E PARA O  
HIPOTÁLAMO NO RATO E ESTUDO DA EXPRESSÃO DOS  
SUBSTRATOS DO RECEPTOR DE INSULINA EM NEURÔNIOS DA VTA  
QUE SE PROJETAM PARA O ESTRIADO**

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## RESUMO

**FERREIRA, J.G.P. Organização das projeções da área tegmental ventral para o complexo VTA-substância negra e para o hipotálamo no rato e estudo da expressão dos substratos do receptor de insulina em neurônios da VTA que se projetam para o estriado.** Tese (Doutorado em Ciências) - Instituto de Ciências Biomédicas da Universidade de São Paulo, São Paulo, 2009.

A área tegmental ventral (VTA) está implicada em mecanismos de recompensa e, mais recentemente, é tida como um centro adicional de detecção de sinais metabólicos periféricos. Na primeira etapa deste trabalho, investigamos as conexões intrínsecas da VTA para o complexo VTA-substância negra utilizando como traçador anterógrado a leucoaglutinina do *Phaseolus vulgaris* (PHA-L). Os resultados obtidos sugerem que a VTA dorsolateral se projeta para ela mesma e para a porção dorsal da substância negra compacta e núcleo retrorubral; a VTA ventrolateral inerva principalmente o núcleo interfascicular; os componentes da VTA caudomedial (núcleos interfascicular, paranigral e caudal linear) estão interconectados; o pólo caudal da VTA envia projeções robustas e bilaterais para praticamente todo o complexo VTA-substância negra, terminando tanto na porção dorsal quanto na porção ventral da substância negra compacta; aposições entre varicosidades imunorreativas para PHA-L e neurônios imunorreativos para tirosina hidroxilase (TH+) foram observadas. Numa segunda etapa, investigamos as projeções da VTA para o hipotálamo. A importância de mecanismos dopaminérgicos no hipotálamo lateral já é reconhecida há tempo, tendo sido implicados na ingestão de alimentos, na indução de preferência condicionada a lugar e na aquisição de respostas condicionadas apetitivas. Os resultados de nosso estudo sugerem que: 1) A VTA se projeta principalmente para a área pré-óptica lateral, a área hipotalâmica lateral, a região subfornical posterior e os núcleos dorsomedial e posterior do hipotálamo. Deve ser ressaltado que a área hipotalâmica lateral é mais densamente inervada em sua porção rostral do que em suas porções tuberal ou posterior. A VTA origina ainda aferências modestas para a área pré-óptica medial e para as regiões perfornical e supramamilar; 2) Há evidências de uma organização topográfica das projeções da VTA para o hipotálamo. Em particular, as projeções para o núcleo dorsomedial e a região subfornical posterior se originam primariamente da VTA caudomedial, sendo que a região rostródorsal da VTA evita totalmente estes distritos hipotalâmicos; 3) Aposições entre terminais imunorreativos para PHA-L e neurônios imunorreativos para orexina ou hormônio concentrador de melanina foram observadas, porém são pouco frequentes; 4) Em experimentos de dupla marcação anterógrada com injeções de amino dextrana biotina no accumbens e PHA-L na VTA, foi observado embricamento destas projeções na área pré-óptica lateral e região anterior do hipotálamo lateral. Numa terceira etapa, investigamos a colocalização do substrato do receptor de insulina do tipo I (IRS-1), do IRS-1 fosforilado e da fosfatidilinositol-3 quinase (PI3K) com TH ou com a subunidade B da toxina colérica (CTb) após sua injeção no estriado. Nossos dados sugerem que: 1) A grande maioria dos neurônios dopaminérgicos do complexo VTA-substância negra expressa IRS-1; 2) Injeções na concha ou no cerne do accumbens resultaram numa porcentagem similar de células duplamente marcadas para CTb/IRS-1. Um número significativo de células foram duplamente marcadas para CTb/PI3K; 3) Injeções no estriado dorsal resultaram em células duplamente marcadas para

CTb/PI3K e CTb/IRS-1 fosforilado; 4) A marcação para IRS-1 foi identificada no núcleo das células, diferentemente do observado por Folli e colaboradores (**J. Neurosci.** 14: 6412-6422, 1994) que relataram esta marcação no citosol.

**Palavras-chave:** Dopamina. Substância negra. Núcleo retrorrubral. Área pré-óptica lateral. Área hipotalâmica lateral. Substratos do receptor de insulina.

## ABSTRACT

FERREIRA, J.G.P. **Organization of the ventral tegmental area projections to the VTA-nigral complex and to the hypothalamus in the rat and VTA neurons projecting to the accumbens express insulin receptor substrates.** PhD thesis (Physiology) - Biomedical Sciences Institute, the University of São Paulo, São Paulo, 2009.

The ventral tegmental area (VTA) is involved in reward mechanisms and, more recently, has been identified as an additional center detecting peripheral metabolic signals. In the first part of this work, the projections from the VTA to the VTA-substantia nigra complex were investigated using the anterograde tracer *Phaseolus vulgaris* leucoagglutinin (PHA-L). The results suggest that the dorsolateral VTA projects to itself and to the dorsal portion of the substantia nigra compacta and retrorubral nucleus. The ventrolateral VTA innervates mainly the interfascicular nucleus. The components of the caudomedial VTA (interfascicular, caudal linear and paranigral nuclei) are interconnected. The caudal pole of the VTA sends robust and bilateral projections to almost the entire VTA-substantia nigra complex, ending in both the dorsal and ventral tiers of the substantia nigra compacta. Appositions between PHA-L immunoreactive varicosities and neurons immunoreactive to tyrosine hydroxylase (TH+) were often observed. In the second part of this work, the VTA projections to the hypothalamus were investigated. The importance of dopaminergic mechanisms in the lateral hypothalamus has long been acknowledged, they are involved in food intake, conditioned place preference, acquisition of appetitive conditioned responses and locomotor activity. The present results suggest that: 1) the VTA projects mainly to the lateral preoptic area and lateral hypothalamic area, the posterior subfornical region as well as to the dorsomedial and posterior hypothalamic nuclei. The lateral hypothalamic area is more densely innervated at rostral levels than at tuberal or caudal levels. The VTA also provides modest inputs to the medial preoptic area, the perifornical area and to the supramammillary region; 2) VTA projections to the hypothalamus display some topographical organization. In particular, projections to the dorsomedial nucleus and posterior subfornical region originate primarily from the caudomedial VTA, whereas the rostradorsal VTA avoids these hypothalamic districts; 3) Appositions between PHA-L immunoreactive varicosities and neurons immunoreactive to orexin or melanin-concentrating hormone were observed, but they are uncommon; and 4) In double labeling experiments with injections of anterograde biotin dextran amine into the accumbens and PHA-L into the VTA, an extensive overlap of these projections was observed in the lateral preoptic area and anterior part of the lateral hypothalamic area. In the third part of this work, we have investigated the co-localization of the insulin receptor substrate type I (IRS-1), IRS-1 phosphorylated and phosphatidylinositol-3 kinase (PI3K) with TH or cholera toxin B subunit (CTb) injected into either the accumbens or the caudate-putamen. Our data suggest that: 1) The vast majority of dopaminergic neurons of the VTA-substantia nigra complex express IRS-1; 2) Injections into the shell or core of the accumbens resulted in a similar percentage of double-labeled cells for CTb/IRS-1. A significant number of cells were double-labeled for CTb/PI3K and 3) Injections in the dorsal striatum resulted in cells that were double-labeled for CTb/PI3K and CTb/IRS-1 phosphorylated, 4) The IRS-1 immunolabeling was localized in the nucleus of cells, unlike the cytosolic labeling observed by Folli and colleagues (J. Neurosci. 14: 6412-6422, 1994).

**Keywords:** Dopamine. Substantia nigra. Retrorubral nucleus. Lateral preoptic area. Lateral hypothalamic area. Insulin receptor substrates.

# PARTE 1 - PROJEÇÕES DA VTA PARA O COMPLEXO VTA-SUBSTÂNCIA NEGRA

## 1.1 INTRODUÇÃO

A área tegmental ventral (VTA) está implicada em mecanismos de recompensa e em processos cognitivos (GOLDMAN-RAKIC, 1999; GOLDMAN-RAKIC *et al.*, 2004; IKEMOTO, 2007). Ela ocupa a região ventromedial do mesencéfalo compreendida entre o núcleo interpeduncular, a substância negra e o núcleo rubro (HALLIDAY e TÖRK, 1986; OADES e HALLIDAY, 1987). Alberga o grupamento dopaminérgico A10 (DAHLSTRÖM e FUXE, 1964; BJÖRKLUND e LINDVALL, 1984) e também numerosos neurônios GABAérgicos (STEFFENSEN *et al.*, 1998; OLSON e NESTLER, 2007).

Suas principais relações anatômicas já foram delineadas em estudos clássicos. A VTA recebe aferências de um grande número de estruturas, a maioria delas do cerne isodendrítico (PHILLIPSON, 1979b; GEISLER e ZAHM, 2005) e dá origem ao sistema mesocorticolímbico, cujos principais alvos são o estriado ventral, o cortex pré-frontal, a área septal, a amígdala e a habênula lateral, entre outras estruturas (FALLON e MOORE, 1978; BECKSTEAD *et al.*, 1979; SWANSON, 1982; BJÖRKLUND e LINDVALL, 1984). Foi ainda demonstrado que as projeções telencefálicas da VTA são topograficamente organizadas. Elas obedecem a um plano de organização médio-lateral, de modo que distritos mediais da VTA inervam regiões mediais do telencéfalo e distritos laterais da VTA inervam regiões laterais do telencéfalo (FALLON e MOORE, 1978; FALLON *et al.*, 1978; BECKSTEAD *et al.*, 1979; KLITENICK *et al.*, 1992) e que setores rostr dorsais da VTA projetam-se preferencialmente para territórios corticais e setores ventrocaudais da VTA, principalmente para áreas subcorticais mesolímbicas (SCHEIBNER e TÖRK, 1987; OADES e HALLIDAY, 1987). Em estudos de rastreamento retrógrado observou-se que as projeções da VTA para o accumbens obedecem a um padrão dorso-ventral invertido de forma que os setores mais dorsais da VTA se projetam para as porções mais ventrais do accumbens e os setores mais ventrais da VTA estão relacionados com os setores mais dorsais do accumbens (BROG *et al.*, 1993; HASUE e SHAMMAH-LAGNADO, 2002). Mais recentemente, Sesack e colaboradores, em uma série de estudos ultraestruturais, forneceram informações adicionais sobre a circuitaria da VTA, que indicam que a sua organização é mais específica do que se acreditava previamente (FIELDS *et al.*, 2007). De fato, aferências para a VTA estabelecem contato sináptico com subpopulações neuronais distintas com base no tipo do

neurotransmissor que elas expressam e no alvo para o qual elas se projetam. Por exemplo, fibras do córtex pré-frontal terminam seletivamente em neurônios dopaminérgicos da VTA que se projetam de volta para o córtex préfrontal e em neurônios GABAérgicos da VTA que inervam o accumbens (CARR e SESACK, 2000).

Apesar da importância funcional da VTA e do sistema mesotelencefálico que ela origina em mecanismos de recompensa cerebral e em processos motivacionais e cognitivos, alguns aspectos desta circuitaria são até hoje pouco conhecidos. Neste trabalho, vamos descrever, em uma primeira etapa, as projeções da VTA para o complexo VTA-substância negra (FERREIRA *et al.*, 2008).

Foi proposto em bases eletrofisiológicas e farmacológicas que neurônios GABAérgicos da VTA, via conexões locais, podem inibir tonicamente presumíveis neurônios dopaminérgicos, ou seja que a liberação de dopamina é controlada em parte por mecanismos desinibitórios (JOHNSON e NORTH, 1992; STEFFENSEN *et al.*, 2006). Entretanto, existem poucos dados na literatura a respeito da circuitaria intrínseca da VTA ou de suas projeções para outros componentes do complexo VTA-substância negra, a saber a substância negra compacta (SNc) e o núcleo retrorubral (RR). Phillipson (1979a) relatou, em um estudo utilizando a técnica de Golgi, que neurônios da VTA às vezes emitem um colateral que termina próximo do corpo celular de origem, porém nem a densidade e nem a organização detalhada destas conexões intra-VTA puderam ser avaliadas neste estudo. Beckstead e colaboradores (1979), em um estudo utilizando a técnica radioautográfica, observaram uma marcação na SNc ipsilateral e em partes adjacentes da substância negra reticulada após injeções na VTA. Entretanto, essa técnica não permite diferenciar terminações axonais de fibras de passagem.

Em termos mais gerais, uma investigação das projeções locais da VTA para o complexo VTA-substância negra tem implicações para compreender o fluxo de informações nos núcleos da base. Embora a VTA seja composta de núcleos citoarquiteticamente distintos (PHILLIPSON, 1979a; OADES e HALLIDAY, 1987), ela é usualmente vista como uma entidade anatômica. Recentemente, Ikemoto (2007), usando como critério a topografia médio-lateral das projeções da VTA para o estriado ventral, subdividiu a VTA em duas regiões principais. A VTA caudomedial, que inclui o núcleo interfascicular, o núcleo caudal linear e o núcleo paranigral, termina seletivamente no estriado ventromedial, e a VTA lateral, correspondendo ao núcleo parabraquial pigmentoso, inerva principalmente o estriado ventrolateral (BROG *et al.*, 1993; HASUE e SHAMMAH-LAGNADO, 2002; DEL FAVA *et al.*, 2007; IKEMOTO, 2007). Evidências da literatura sugerem que estes dois sistemas

mesoestriatais têm funções diferentes em mecanismos de recompensa. O sistema mesoestriatal ventromedial está envolvido no aprendizado de uma associação estímulo-resultado e o sistema mesoestriatal ventrolateral, no aprendizado de uma associação estímulo-ação (IKEMOTO, 2007). Através de um elo sináptico na VTA lateral, o estriado ventromedial pode influenciar a atividade do estriado ventrolateral, que por sua vez, através da SNc, pode afetar a atividade do estriado dorsal (NAUTA e DOMESICK, 1978; HABER *et al.*, 2000). Assim, através de alças espiraladas estriado-nigro-estriatais, aspectos motivacionais podem interagir com processos cognitivos e estes com funções motoras. A análise das projeções da VTA para o complexo VTA-substância negra poderia esclarecer se populações neuronais relacionadas com o mesmo domínio estriatal estão preferencialmente interconectadas e/ou se as conexões observadas podem mediar interações entre populações neuronais que se projetam para diferentes domínios estriatais.

Obs.: Esta primeira etapa do trabalho foi publicada recentemente – FERREIRA *et al.*, 2008.



#### *1.4.9 Marcação anterógrada de PHA-L combinada à imunistoquímica para TH*

A análise da série processada para dupla reação imunistoquímica para PHA-L/TH confirmou que a marcação anterógrada produzida por injeções na VTA está localizada em distritos ricos em TH contendo os grupamentos A8, A9 e A10. Foram observados dois tipos diferentes de fibras: uma com pequeno calibre e varicosidades finas (Figura 13D) e outra de calibre mais grosso e com varicosidades maiores (Figura 13B; ver também Gerfen *et al.*, 1987a). Varicosidades dos 2 tipos foram, às vezes, vistas apostas a um dendrito ou pericário imunorreativo para TH na VTA, SNc e RR (Figura 13).

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