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Striatal dopamine neurotransmission: Regulation of release and uptake

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ABSTRACT

Dopamine (DA) transmission is governed by processes that regulate release from axonal boutons in the forebrain and the somatodendritic compartment in midbrain, and by clearance by the DA transporter, diffusion, and extracellular metabolism. We review how axonal DA release is regulated by neuronal activity and by autoreceptors and heteroreceptors, and address how quantal release events are regulated in size and frequency. In brain regions densely innervated by DA axons, DA clearance is due predominantly to uptake by the DA transporter, whereas in cortex, midbrain, and other regions with relatively sparse DA inputs, the norepinephrine transporter and diffusion are involved. We discuss the role of DA uptake in restricting the sphere of influence of DA and in temporal accumulation of extracellular DA levels upon successive action potentials. The tonic discharge activity of DA neurons may be translated into a tonic extracellular DA level, whereas their bursting activity can generate discrete extracellular DA transients.

Contents

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1. Regulation of dopamine release

Dopamine (DA) neurotransmission is generally initiated by the fusion of synaptic vesicles in axonal boutons, with the exceptions of release by amphetamine-like drugs that can release DA *via* reverse transport through the DA uptake transporter (DAT) [1,2], and DA release from dendrites, which is widely suspected to occur *via* fusion of specialized secretory organelles [3]. This process is regulated at many levels, including DA synthesis, uptake and vesicular transport, as well as by Ca^{2+} homeostasis and regulatory exocytotic proteins. In addition, neurotransmitter receptors on DA neurons, axons, and dendrites provide feedback, regulate DA release, and in some conditions locally drive DA release.

1.1. Dopamine release by synaptic vesicle fusion

1.1.1. Quantal release and detection

In 1950, Bernard Katz and Paul Fatt published recordings of random electrical "noise" consisting of spontaneous small "action potentials" (a term now used quite differently) at frog neuromuscular junction they compared to "fluctuations in the number of light quanta which strike the [photo]receptor cells" [4]. These "miniature end plate potentials" required extracellular Ca^{2+} and were exacerbated by high osmolarity [5]. The events fit a Poisson distribution, which simulates the probability of random occurrences of multiple basic events [6], indicating that neurotransmission occurs in multiples of a "quantal" unit. They conjectured that "the apparatus for the release of acetylcholine (ACh) at a junction is subdivided into a large number of units (at least 100), each of which is able to operate independently of the rest" [7].

In contrast to ionotropic ACh receptors, DA primarily activates G protein-coupled receptors that do not produce small rapid currents, and so a means to detect quantal DA release was elusive. An effective approach was provided by electrochemical catecholamine detection, introduced by Ralph Adams and colleagues [8–10]. These methods were improved by the introduction of carbon-fiber microelectrodes for detection of catecholamines by Francois Gonon [11] and Michael Armstrong-James and Julian Millar [12,13]. Armstrong-James and Millar [14] also developed the method of fast-scan cyclic voltammetry (FCV) with carbon-fiber electrodes, which is widely used for monitoring DA release and uptake *in vivo* and in *ex vivo* brain slices.

The first analysis of quantal release of catecholamines used large secretory vesicles from the adrenal gland. Extracts from adrenal cells provided the original evidence for secretory transmission [15]. In 1990, Mark Wightman and colleagues [16] used amperometry to detect quantal catecholamine release from adrenal cells. In contrast to postsynaptic recording, amperometric recording indicates directly the number of molecules released and the duration of a quantal release event, which in adrenal chromaffin cells is about $\sim 10^6$ molecules over the course of $\sim 10^{-1}$ s.

Amperometric recording was then adapted to record from axonal terminals of cultured midbrain DA neurons. Synaptic vesicles in these axons are ~40 nm in diameter, with a volume that is ~1000-fold smaller than that of adrenal chromaffin granules, with proportionally smaller quantal events that are of shorter duration than those from adrenal cells [17,18]. The released catecholamine was identified as DA based on: (1) blockade by reserpine, a vesicular monoamine transporter type 2 (VMAT2) inhibitor; (2) colocalization with tyrosine hydroxylase (TH); (3) the potential required for DA oxidation; (4) absence of detection from neurons that lack DA; and (5) elevation of quantal size following exposure to L-DOPA, a DA precursor, or increased VMAT2 expression. The shape of the majority of quantal DA events in neurons closely fit a simulation of transmitter diffusion through a pore [19], but some release events that deviate from such simple shapes (see Section 1.1.3).

In cultured DA neurons, quantal events have been recorded from boutons in axons, and from acutely dissociated DA somata [20], which may represent quantal somatodendritic release events or release of synaptic vesicle precursors that would have been trafficked to axons. Release events have also been found in acute midbrain slices, although it is difficult to exclude release from nearby DA or serotonin terminals [21]. It seems likely that occasional DA secretion occurs at cell bodies, as VMAT2 transfection of hippocampal neurons can produce quantal